PEDIATRIC CLINICS OF NORTH AMERICA

Medical
610.5
P364

© 1956, BY W. B. SAUNDERS COMPANY

COPYRIGHT UNDER THE INTERNATIONAL COPYRIGHT UNION

All Rights Reserved. This book is protected by copyright.
No part of it may be duplicated or reproduced
without written permission from the publisher.

MADE IN U.S.A. PRESS OF W. B. SAUNDERS COMPANY, PHILADELPHIA

Library of Congress Catalog Card Number: 54-6097

CONTRIBUTORS

MAY ISSUE

JOHN M. ADAMS, M.D., PH.D., F.A.A.P. Professor and Chairman of Department of Pediatrics, University of California at Los Angeles; Honorary Consulting Staff, Santa Monica Hospital; Visiting Consultant in Pediatrics, St. John's Hospital; Consultant in Pediatrics, Harbor General Hospital, Los Angeles; Consultant in Infectious Diseases, Veterans Administration Hospital, Long Beach, California.

BURTIS B. BREESE, M.D., F.A.A.P. Assistant Professor of Pediatrics, University of Rochester School of Medicine and Dentistry; Visiting Pediatrician, Strong Memorial Hospital, Syracuse, New York.

MEREDITH F. CAMPBELL, M.D., F.A.A.P. Emeritis Professor of Urology, New York University School of Medicine; Consulting Urologist, Bellevue Hospital, New York City, and St. Francis Hospital, Miami Beach, Florida.

MERL JOHN CARSON, M.D., F.A.A.P. Professor of Pediatrics, University of Southern California School of Medicine; Medical Director, Children's Hospital Society of Los Angeles.

JEAN DUFRENOY, Sc.D. Professor, Conservatoire National des Arts et Métiers, Paris, France.

GEORGE M. EISENBERG, D.Sc. Chief, Division of Bacteriology and Serology, Department of Laboratories, Philadelphia General Hospital, Philadelphia.

NATALIA S. FELIX, M.D. Research Fellow, Department of Pediatrics, Cedars of Lebanon Hospital, Los Angeles.

FREDERICK C. FINK, PH.D. Coordinator, Hospital Laboratory Advisory Service, Chas. Pfizer & Co., Inc., Brooklyn.

HARRISON F. FLIPPIN, M.D. Professor of Clinical Microbiology, University of Pennsylvania Graduate School of Medicine, Philadelphia.

WILLIAM L. HEWITT, M.D. Associate Professor of Medicine (Infectious Diseases), University of California at Los Angeles; Attending Specialist, Internal Medicine, Wadsworth Hospital, Veterans Administration Center; Regular Staff, University of California Hospital, Los Angeles.

ERNEST JAWETZ, M.D., PH.D. Professor of Microbiology and Lecturer in Medicine and Pediatrics, University of California School of Medicine; Visiting Physician, Uni-

versity of California Hospitals; Attending Pediatrician, San Francisco County Hospital, San Francisco.

B. M. KAGAN, M.D., F.A.A.P. Clinical Professor of Pediatrics, University of California at Los Angeles; Director, Department of Pediatrics, Cedars of Lebanon Hospital, Los Angeles.

SAMUEL KARELITZ, M.D., PH.D., F.A.A.P. Associate Professor of Clinical Pediatrics, Columbia University College of Physicians and Surgeons; Chief of Pediatrics, Long Island Jewish Hospital, New Hyde Park; Attending Pediatrician, Mt. Sinai Hospital, New York City.

DAVID T. KARZON, M.D. Assistant Professor of Pediatrics and Assistant Professor of Virology, University of Buffalo School of Medicine; Virologist, Children's Hospital, Buffalo.

HARRY KING, M.D., F.A.A.P. Staff Pediatrician, Long Island Jewish Hospital, New Hyde Park, New York.

R. KOCH, M.D. Instructor in Pediatrics, University of Southern California School of Medicine; Out-Patient Director, Los Angeles Children's Hospital, Los Angeles.

ROBERT M. KOHLENBRENER, M.D., M.S. Chief Resident, Department of Pediatrics, Michael Reese Hospital, Chicago.

RALPH H. KUNSTADTER, M.D., F.A.C.P., F.A.A.P. Assistant Professor of Pediatrics, Northwestern University Medical School; Acting Chairman of the Department of Pediatrics, Michael Reese Hospital, Chicago.

ERWIN NETER, M.D. Assistant Professor of Pediatrics and Assistant Professor of Bacteriology, University of Buffalo School of Medicine; Director, Laboratory of Bacteriology, Children's Hospital; Consultant Bacteriologist, Roswell Park Memorial Institute, Buffalo.

ROBERTSON PRATT, PH.D. Professor of Pharmacognosy and Antibiotics, University of California Medical Center, San Francisco.

SYDNEY ROSS, M.D., F.A.A.P. Assistant Clinical Professor of Pediatrics, Georgetown University Medical School; Research Associate, Research Foundation of Children's Hospital; Associate Attending Physician, Children's Hospital, Washington, D.C.

AUGUSTO SCHUSTER, M.D. Fellow, Kellog Foundation; Research Fellow in Pediatrics, Children's Medical Center, Boston, 1955; Medical House Staff, Hospital Roberto del Rio, Santiago, Chile.

EMITT H. SHOEMAKER, M.D. Instructor in Medicine, Baylor University College of Medicine; Staff Member, Herman and Jefferson Davis Hospitals, Houston.

HARRY SHWACHMAN, M.D., F.A.A.P. Assistant Professor of Pediatrics, Harvard Medical School; Physician, Chief of Division of Clinical Laboratories, and Chief of Clinical Nutritional Clinics, Children's Medical Center, Boston.

MARGARET H. D. SMITH, M.D. Associate Professor of Pediatrics, New York University College of Medicine, New York City.

J. W. STRODE, M.D. Medical Department, Pfizer Laboratories, Brooklyn.

HART E. VAN RIPER, M.D., F.A.A.P. Medical Director, National Foundation for Infantile Paralysis, New York City.

ELLARD M. YOW, M.D. Associate Professor of Medicine, Baylor University College of Medicine; Attending Physician, Herman, Methodist and Jefferson Davis Hospitals; Consultant in Infectious Diseases, Veterans Administration Hospital, Houston.

CONTENTS

SYMPOSIUM ON ANTIMICROBIAL THERAPY

Foreword	*B. M. Kagan, M.D.*	221
Mechanism of Action of Antibiotics: Current Knowledge	*Robertson Pratt, Ph.D.* *Jean Dufrenoy, Sc.D.*	223
The Synthetic Antimicrobial Agents: Applied Pharmacology	*Harrison F. Flippin, M.D.* *George M. Eisenberg, D.Sc.*	235
Penicillin: Applied Pharmacology	*Sydney Ross, M.D.*	259
Streptomycin and Dihydrostreptomycin: Applied Pharmacology	*Harry King, M.D.* *Samuel Karelitz, M.D.*	279
The Tetracyclines: Applied Pharmacology	*Harry Shwachman, M.D.* *Augusto Schuster, M.D.*	295
Erythromycin and Related Antibiotics: Applied Pharmacology	*Emitt H. Shoemaker, M.D.* *Ellard M. Yow, M.D.*	305
Chloramphenicol: Applied Pharmacology	*Natalia S. Felix, M.D.*	317
Polymyxin, Neomycin and Bacitracin: Applied Pharmacology	*Ernest Jawetz, M.D.*	329
Combinations of Antimicrobial Agents in Pediatric Practice	*Frederick C. Fink, Ph.D.* *J. W. Strode, M.D.*	345
Diagnosis and Antimicrobial Therapy in Infections of the Respiratory Tract	*John M. Adams, M.D.* *William L. Hewitt, M.D.*	353

Antimicrobial Therapy in Genitourinary Tract Infections	*Meredith F. Campbell, M.D.*	369
Management of Bacterial Meningitis in Children	*M. J. Carson, M.D.* *R. Koch, M.D.*	377
Antimicrobial Therapy in Cardiovascular Infections	*Burtis B. Breese, M.D.*	399
Antimicrobial Therapy in Gastrointestinal Tract Infections	*Ralph H. Kunstadter, M.D.* *Robert M. Kohlenbrener, M.D.*	407
Practical Management of Tuberculosis	*Margaret H. D. Smith, M.D.*	427
Toxicology of the Antibiotics	*B. M. Kagan, M.D.*	439
Pediatric Dosages and Routes of Administration of Antibiotics	*Erwin Neter, M.D.* *David T. Karzon, M.D.*	447

ANNUAL STATEMENT ON POLIOMYELITIS

Poliomyelitis, 1956	*Hart E. Van Riper, M.D.*	457
Index		483

FOREWORD

B. M. KAGAN, M.D.

The student of antimicrobial therapy must be prepared for change. New antibiotics are being discovered each year. Perhaps even more important, the bacteria themselves are constantly changing in their sensitivity to those antibiotics which are in use. The human host in turn is constantly changing in sensitivity to the same bacteria, to newly developed flora and also to the antimicrobial agents themselves.

Because of constant change of interrelationships among the host, the organisms and these drugs, those who work with the practical application of such potent therapeutic agents must be familiar with their pharmacology, with the natural history of infection, with the history of infection as modified by these agents, and also with their possible effects on the human host.

To this end the approach in this volume has been to present, first, the pharmacologic background of antibiotics, the relation of the various agents to bacterial infection, and the specific diseases in which they may be found useful. Finally there are clinics on toxicology and on dosages and routes of administration.

It is hoped that this material can be utilized as a ready reference manual on antimicrobial therapy. The object has been to present important information as succinctly as possible for the benefit of the many busy physicians who are responsible for the care of the infants and children in this country.

I would like to express sincere appreciation to the authors of the clinics in this volume. They have been generous with their time and interest in preparing these practical summations of current knowledge for the specific use and benefit of those in active practice. Their efforts are reflected in the quality of the material presented.

MECHANISM OF ACTION OF ANTIBIOTICS

Current Knowledge

ROBERTSON PRATT, PH.D.

JEAN DUFRENOY, SC.D.

The objective in clinical use of antibiotics is primarily to cure infectious diseases, although prophylactic use is acquiring importance in some fields. Whether the drugs are used therapeutically or prophylactically, the most significant feature from the practical viewpoint is the total complex of the effects of the antibiotic agent in vivo: these include the diversified interactions of the host-drug system, of the drug-pathogen system, of the host-pathogen system, and finally the complex interactions among these several systems. The host-drug and host-pathogen systems are subjects for consideration by the pharmacologist and immunologist, respectively, and are discussed in later clinics. The present clinic deals primarily with the drug-pathogen system, but includes also brief discussion of pertinent aspects of the total complex of host-drug-pathogen interactions.

The drug-pathogen system is amenable to study in vitro, and, indeed, most of the current knowledge of the mechanisms of action of antibiotics has been derived from such studies, although important contributions have been made also from studies with appropriately chosen animal tissues and fluids. For example, morphologic changes induced by penicillin in *Proteus vulgaris*, and Enterobacteriaceae in general, may be made in the peritoneal fluid of mice under conditions that more closely resemble clinical circumstances than do those that generally prevail in the conventional culture media in test tubes or on agar plates.[8] But valuable as studies in vivo are, experiments in vitro offer distinct advantages in attempts to ascertain the chemical and physical

modus operandi of antibiotics on bacteria. In the test tube or on agar plates it is possible to investigate, in a chemically defined medium, the effects of drugs on isolated enzyme systems or to study the response of intact organisms of a given microbial strain to graded doses of a single drug or to mixtures of drugs. Alternatively, the effects of one or more drugs on a single strain or on mixtures of two or more strains may be analyzed. The latter situation may be more analogous to conditions that exist in common clinical use, in which mixed infections often are encountered.

Much is known about the biochemical changes that some antibiotics induce in microorganisms, but in many instances it is not known whether these changes are responsible for the inhibitory effects of the drugs on bacterial growth and reproduction or merely are concomitant consequences of some more fundamental effects that still remain to be discovered. At present it is impossible to define precisely a single mechanism of action for a given antibiotic-pathogen system. It seems clear that several effects occur concomitantly, and perhaps it is the total complex of these effects, rather than any one alone, that is responsible for the inhibitory action of the antibiotics and for their clinical usefulness. In this clinic no attempt is made to discuss all the clinically useful antibiotics or to review all the pertinent literature: discussion is confined to those antibiotics and metabolic processes for which clear-cut data are available. Much of the literature has been reviewed previously by Pratt and Dufrenoy.[25]

SYSTEMIC ANTIBIOTICS

The effects of antibiotics, such as penicillin and others that are commonly used for systemic medication, may be discussed in terms of morphologic, metabolic and antigenic changes. However, all these ultimate manifestations of the action of the drugs stem from alteration of one or more enzymatically controlled functions. As a first example, penicillin may be contrasted with streptomycin.

Penicillin and Streptomycin

In sensitive organisms it is dehydrogenase-dependent reactions that are affected first by penicillin. Streptomycin, on the other hand, seems to exert a main effect on reactions that are activated by the functioning of oxidases. Evidence that strongly suggests the involvement of glutathione in the mechanism of penicillin action on sensitive bacteria has been published,[26] and it has been pointed out that "the over-all effect of penicillin may be traceable ultimately to dehydrogenation of reduced glutathione to oxidized glutathione resulting largely from the increased

rate of metabolism that is induced by appropriately low concentrations of penicillin. The most efficient . . . concentration of penicillin may be . . . one which promotes dehydrogenation faster than rehydrogenation can restore —SH groups."[25] These conclusions have been substantiated by more recent research on the effects of penicillin on the synthesis of proteins by living bacteria and on the interaction of penicillin with metals, cysteine and glutathione.[3] Glutathione probably is involved also in the response of some penicillin-resistant organisms, such as *Escherichia coli,* to penicillin. In appropriate concentrations, glutathione nullifies the slight depressing effect of low concentrations of the antibiotic, but, conversely, seems to sensitize the microorganisms to larger doses of it.[24]

The difference between penicillin-sensitive and penicillin-resistant organisms has been correlated with the ability of the bacteria to maintain an adequate balance of functioning sulfhydryl groups in the presence of the antibiotic. For instance, in *Micrococcus pyogenes* var. *aureus* the activity of succinic dehydrogenase (an —SH enzyme) becomes more prominent as penicillin resistance increases, and analysis reveals that the resistant variants are richer in —SH groups than the sensitive strains.[2] In *E. coli,* normally considered resistant to penicillin, there likewise is a decrease in —SH content upon exposure to penicillin, but, even with this loss, the organism apparently maintains an —SH level sufficiently above the minimum required for survival to enable the bacteria to continue growth and reproduction.[2]

In contrast to the situation that obtains with penicillin, of all the enzymes known to be inhibited by streptomycin, diamine oxidase is among the most sensitive.[45] This has been demonstrated not only in organisms sensitive to penicillin, but also in pathogenic mycobacteria and in *Pseudomonas aeruginosa.* In species of *Pseudomonas* and in *E. coli* the effects of streptomycin have been ascribed also to its ability to inhibit a reaction involving oxaloacetic and pyruvic acids, which play an essential role in aerobic respiration of sensitive organisms.[40, 41]

In view of the widespread use of streptomycin in tuberculosis, it would be interesting to know whether the antibiotic induces a similar inhibitory effect on oxaloacetate and pyruvate conversion in *Mycobacterium tuberculosis.* Although technical difficulties have interfered with conclusive demonstration of this action in *M. tuberculosis,* it has been shown that in this organism streptomycin blocks, or at least retards, complete oxidative breakdown of fatty acids containing 12 or more carbon atoms. However, the antibiotic does not impede oxidation of saturated fatty acids (with an even number of carbon atoms in the chain) as long as the chain length does not exceed 10 carbon atoms. It has been concluded that initial oxidation of the longer acids is not impeded, but that it is oxidation of their degradation products that is

affected.[22] Acquisition of streptomycin resistance by *M. tuberculosis* is associated with the development of enzymes that enable organisms to carry out these oxidative reactions irrespective of the presence of the antibiotic.

Consideration of the substrates for aerobic respiration reveals another aspect of the comparative mechanisms of action of penicillin and streptomycin. The effect of penicillin on sensitive bacteria has been correlated with its ability to block utilization of guanylic and uridylic acids,[3, 9, 10, 17] but such effects have not been noted with streptomycin.

Penicillin and streptomycin may also be contrasted in that they intervene at different steps in the chain of reactions involved in degradation of ribose nucleic acid derivatives.

Penicillin acts primarily on gram-positive organisms during their logarithmic phase of growth. This phase normally is characterized by rapid utilization of reserves of ribose nucleic acid complexes which must be stockpiled by the organisms before they can start rapid proliferation. Penicillin does not interfere with biosynthetic accumulation of ribose nucleic acid reserves, nor with the initial phases of catabolism, characterized by depolymerization to mononucleotides. But it does prevent subsequent utilization of mononucleotides by blocking alkaline phosphatases, acting as mononucleotidases, which are responsible for the catabolism of mononucleotides, notably of their guanylic and uridylic acid components. The innocuity of penicillin for the metabolic reactions of the host may be correlated with the fact that mononucleotidase in mammals differs from that in penicillin-sensitive microorganisms.[14]

In contrast to the foregoing, streptomycin, acting on gram-negative organisms, blocks depolymerization of ribose nucleic acid reserve material and causes it to leach out of the cells, leaving only ghosts composed of desoxyribose nucleic acid inclusions. This observation is compatible with the view that dihydrostreptomycin (and presumably streptomycin) exert their inhibitory effects by "irreversibly binding stored bacterial high energy phosphate bonds."[11] The net effect of such binding might be to render the bacteria incapable of normal biosynthesis of high energy bonds and even of carrying out the initial reactions that lead to biosynthesis of the bonds. The nucleic acid groups involved in the formation of complexes with streptomycin have been reviewed[25] and recently have been reinvestigated.[5]

Enhancement of Penicillin Efficiency by Traces of Cobalt

It has been known for some time that culturing *Micrococcus pyogenes* var. *aureus (Staphylococcus aureus)* and certain other organisms on a medium enriched with traces of cobalt increases their sensitivity

to penicillin.[7, 38] The effect is not limited to normally penicillin-sensitive species. Organisms such as *E. coli* and *Eberthella typhosa*, generally considered resistant to the antibiotic, may be brought within the antibiotic spectrum of penicillin when exposed, previously or concomitantly, to traces of cobalt.[27, 38] Otorhinolaryngologists, notably in Italy and central Europe, have taken clinical advantage of this fact in treating suppurative lesions of the ear. Widest applications, however, have been made in veterinary medicine,[39] especially on poultry farms, for the control of *Salmonella pullorum*, which usually is considered penicillin-resistant.

Recent research has revealed interesting information about the possible mechanism of action of the cobalt and penicillin effect. Arginine has been shown to delay infection of chicks by *S. pullorum*.[32] This observation ties in with the fact that traces of cobalt have a specific effect on arginase[12] and that cobalt reverses the inhibitory action of penicillin (and certain other antibiotics) on the enzyme.[30] Tending to confirm the earlier observations that there is an optimum (but exceedingly low) concentration of cobalt that enhances penicillin action and that higher concentrations are less effective (or ineffective),[27, 38] it has been shown recently that high concentrations of cobalt inhibit arginase.[30]

Relatively high concentrations of cobalt alone have therapeutic value, presumably through their hematopoietic effects, in some suppurative infections.[29] However, the concentrations required to induce potentiation of penicillin are well below those that demonstrably affect hematopoiesis or inhibit bacterial growth.[27] It may be significant with regard to the enhancement of penicillin activity by traces of cobalt that in bacteria cultured in a medium containing the metal ion (Co^{++}) there is a "marked increase in the amount of . . . 'activatable' [*sic*] or 'potential' enzyme" (namely, pyrophosphatase).[21] Although the precise mechanisms are not known, this observation seems to correlate with the fact that alkaline phosphatase activity and nucleotide metabolism are involved in the mechanism of penicillin action against bacteria.

Chloramphenicol

Several bacterial enzymes are inhibited by chloramphenicol. Notable among these are certain alkaline phosphatases which act as esterases. In sensitive bacteria exposed to this antibiotic there also is inhibition of dipeptide synthesis. These effects are induced by concentrations of drug which do not interfere with biosynthesis of nucleic acid complexes or with their depolymerization. However, because of derangements elsewhere in the metabolic machinery, the mononucleotides accumulate in excess. Thus one of the ultimate cytochemical effects of chlor-

amphenicol is similar to a major manifestation of inhibition by penicillin, although the end results are brought about through different mechanisms.

Contributing to the metabolic derangement of organisms exposed to chloramphenicol are impaired ability to assimilate ammonia, suppression of oxidative activity, and abnormal utilization of glutamate;[37, 43] these effects, which result in impaired protein synthesis and utilization, have been reviewed.[35, 44]

The Tetracyclines

The tetracyclines, like chloramphenicol, also inhibit synthesis of peptides. However, chloramphenicol appears to be more specific in its action: low concentrations which do not inhibit nucleotide synthesis interfere with elaboration of protein. On the other hand, the tetracyclines seem to inhibit both functions indiscriminately.*

Although chlortetracycline and oxytetracycline both interfere with nucleotide metabolism, their effects seem to differ in detail. Chlortetracycline has been reported to dissociate oxidation and phosphorylation mechanisms,[16] while oxytetracycline, reminiscent of penicillin, inhibits utilization of mononucleotides. Further evidence, although indirect, that the actions of chlortetracycline and oxytetracycline are similar, but have minor differences, is afforded by the oft-repeated observation that in acquiring resistance to one of these antibiotics organisms frequently manifest partial increase in resistance to the other one also.

Indeed, from the clinical viewpoint the problem of sensitivity vs. resistance is one of the most important aspects of antibiotic therapy, regardless of which antibiotic is being given.

It was pointed out earlier that resistance of gram-positive organisms to penicillin is correlated with the level of —SH groups. Sulfhydryl-bearing compounds are important also in determining resistance to chlortetracycline. However, in this instance it is the optical configuration of the molecule rather than the —SH groups per se that is important. This conclusion results from studies in vitro on the inhibitory effect of chlortetracycline on the microbial enzymes involved in the reduction of aromatic nitro compounds to the corresponding arylamines. The reductases involved in these reactions act only in the presence of cysteine; but the reductase from organisms sensitive to the antibiotic operates most efficiently in the presence of levo-cysteine, whereas dextro-cysteine is most effective in promoting the reaction when it is catalyzed by the enzyme isolated from resistant organisms.[33]

* Most of the studies on mechanism of action of tetracyclines have been conducted with chlortetracycline (Aureomycin) and with oxytetracycline (Terramycin). However, it is assumed that tetracycline itself functions in essentially the same manner.

It may be significant that there are several sites in the molecular structures of the tetracyclines that should be expected to be amenable to chelation with metal ions[42] and that an affinity of both chlortetracycline and oxytetracycline for such ions has been demonstrated experimentally.[1, 28] However, bacteriologic evidence to substantiate chelation as a contributory mechanism of action of the tetracyclines is lacking.

ANTIBIOTICS USED PRINCIPALLY FOR LOCALIZED INFECTIONS*

Polymyxins

The antibiotics discussed thus far are regarded as affecting the microorganisms primarily from within, i.e., after absorption. There are, however, other antibiotics which, although they may exert biochemical effects *within* the organisms, also exert important effects at the surface of the bacteria. Among these are subtilin[18] and the polymyxins: indeed, differences in rate of adsorption on the surface have been correlated with differences in resistance to the latter group of antibiotics.[19] Similarly, the apparent inhibitory effect of certain divalent cations (magnesium, cobaltous, ferrous and manganous) on polymyxin has been shown to be due to their interfering with adsorption (and absorption?) of the antibiotic rather than to direct inactivation of it.[20]

Tyrothricin

In contrast with the systemic antibiotics (the initial action of which on bacteria is effected biochemically), tyrothricin, by virtue of its tyrocidin content, probably exerts its primary action through physical means, namely, by disrupting the structural integrity of the cell. Consequently, dehydrogenases cease to function and ATP (adenosine triphosphate) and phosphate are released from the organisms to the surrounding medium. In contrast with penicillin, streptomycin and a number of the other "systemic antibiotics," tyrothricin is as effective against resting bacteria as against those that are actively metabolizing and proliferating. The gramicidin component of tyrothricin exerts a biochemical action in that it inhibits the transphosphorylation processes required for formation of ATP. The fact that gramicidin and penicillin block different enzyme systems involved in the same over-all biochemical chain of events may account for the synergistic effect that occurs when the two antibiotics are used concurrently.

* Among these antibiotics are several (polymyxin, neomycin, bacitracin, and so forth) which are sometimes used systemically, but which, because of their toxicity, generally are limited to topical application, specific use in the gastrointestinal tract, direct instillation into wounds or into the eye, or in other forms of essentially local medication. They may be used therapeutically or prophylactically.

HOST-DRUG-PATHOGEN INTERACTIONS

It is advantageous in trying to understand mechanisms of action of antibiotics to study the drug-pathogen interactions as in the preceding paragraphs. However, in terms of ultimate clinical use it is the more complex host-drug-pathogen system that is involved. Some of the observations made on systems in vitro have direct application in clinical practice. For example, when penicillin, erythromycin, the tetracyclines and certain other antibiotics are introduced into whole blood in vitro, the drugs are absorbed rapidly by the erythrocytes and then slowly released to the serum.[34] This suggests possible practical application in connection with blood banks. Stored blood treated with an appropriate antibiotic, on being transfused to a patient, will provide, through gradual release from the erythrocytes, a therapeutic concentration of the antibiotic for as long as 24 hours.[34]

Closely related to the cytochemical changes induced in microorganisms by exposure to antibiotics are clinically important changes in the biosynthesis of enzymes and in antigenicity. Studies in vitro on the effect of penicillin on the production of hyaluronic acid and hyaluronidase by hemolytic streptococci[6, 31] have afforded a basis for understanding some of the secondary benefits in vivo observed during penicillin therapy. Hemolytic streptococci are common secondary concomitants of infections due to *Corynebacterium diphtheriae*, and it is now recognized that penicillin therapy in diphtheria is beneficial not only because of the direct effect of the antibiotic on the causal agent of the disease, but also because of its inhibitory effect on the streptococci which secrete hyaluronidase that acts as a spreading agent for the diphtheria toxin.

Similarly, observations in vitro on the effects of antibiotics on antigen production by different pathogens have clinical implications for dosage regimens and duration of therapy. For example, typhoid organisms (*Eberthella typhosa*) exposed to chloramphenicol, either in vitro or by treatment of the patient with the drug, induce a lower antibody titer than do normal organisms. Moreover, the antibody titer elicited by chloramphenicol-treated *E. typhosa* decreases much more rapidly than the titer obtained with organisms not exposed to the antibiotic. This may account in part for the relapses or reinfections that sometimes occur after an attack of typhoid fever has yielded in five or six days to chloramphenicol therapy.

Streptococci exposed to penicillin afford other examples of altered antigenicity. For instance, in acquiring resistance to penicillin (through successive transfers), type 24 group A hemolytic streptococci lose completely the ability to produce the M antigen, and type 28 group A organisms lack the type-specific R antigen.[6, 31] The latter organisms also fail to produce proteinase. The loss of type-specific antigens prob-

ably is due to altered protein metabolism caused by failing ability of the organisms to produce antigen or to store it.[6]

The close relation between protein synthesis and immunologic phenomena, of course, is not limited to the effects of antibiotics on bacteria. For example, antibody formation, as well as protein synthesis, is inhibited in patients receiving ACTH and cortisone.[13] In view of the demonstrated effect of certain antibiotics in reducing the antigenicity of some microbial pathogens (an effect which probably is more widespread than has been generally recognized) and the depressing action of at least some corticosteroid hormones on antibody formation, one is led to question seriously the wisdom of joint use of corticosteroids and antibiotics that has been advocated recently in numerous systemic infections. The former empirical dictum that corticosteroid therapy should be suspended during periods of antibiotic therapy seems to have a sound immunologic basis. However, in some circumstances (e.g., in rampant or fulminating infections) judicious use of combined hormonal and antibiotic therapy may be justified. Indications and contraindications for such therapy have been reviewed recently.[13a]

Antibiotic-induced changes in antigenicity sometimes are associated with secondary changes in the ability of the organisms to resist phagocytosis. Thus the efficiency of chloramphenicol in the treatment of typhoid fever has been correlated with decreased resistance of the causal organism to phagocytosis.[15] Similar changes have been shown to occur in bacteria exposed to the low concentrations of tetracyclines used as feed supplements for poultry and certain other animals, thus reducing the hazard of bacteremia or tissue infections from organisms that might cross the intestinal barrier and become established elsewhere. The latter observations from animal husbandry may be of significance in pediatrics. There have been occasional reports that administration of low doses of tetracyclines to premature infants for a few days after birth may prevent excessive ponderal loss,[23, 36] although other investigators have noted no such benefit and have called attention to the potential hazards involved.[4]

SUMMARY

The action of penicillin and of several other antibiotics against sensitive bacteria is exerted most effectively on organisms in the logarithmic phase of growth, when sensitiveness to physical agents (heat, ultraviolet radiation, and the like) also is maximal. Inimical effects during the logarithmic phase may be assumed to result from interference with enzyme systems, particularly with those involved in hydrogen and phosphorus transfer.

Penicillin inhibits dehydrogenases, whereas streptomycin intervenes

more specifically in processes dependent on oxidases. Both antibiotics disrupt the normal chain of events in nucleotide catabolism, although at different levels in the series of reactions.

Chloramphenicol and the tetracyclines also interfere in nucleotide and in dipeptide synthesis. The former also suppresses oxidative activity and impairs ability of the organisms to utilize glutamate normally. The tetracyclines may be less specific than chloramphenicol in some of their biochemical targets. Tetracyclines seem to inhibit both nucleotide synthesis and elaboration of protein indiscriminately, but appropriate concentrations of chloramphenicol inhibit protein anabolism without significantly altering elaboration of nucleotides.

Other antibiotics, notably some that are used exclusively or primarily for localized therapy, exert physical as well as biochemical effects. Examples are tyrothricin, bacitracin and polymyxin, all of which exert their main effects at the cell surface. Tyrothricin disrupts the structural integrity of the cell wall; polymyxin and probably bacitracin affect adsorption and absorption phenomena at the cell surface.

The clinical import of some of the fundamental effects of antibiotics on biochemical reactions, e.g., the relation between impaired protein synthesis and antigenicity, is pointed out.

REFERENCES

1. Albert, A.: Affinity of Terramycin and Aureomycin for Metallic Cations. *Nature*, 172:201, 1953.
2. Akiba, T., and Ishii, K.: Changes in the Sulfhydryl Content of Resistant Bacteria to Chemotherapeutics. II. Studies on Penicillin-Resistant Bacteria. *Japan. J. Exp. Med.*, 22:249, 1952.
3. Carr, L. K., and Macheboeuf, M.: L'action de la pénicilline sur le métabolisme protidique dans les cellules proliférantes des bactéries. *Ann. Inst. Pasteur*, 87:585, 1954.
4. Coodin, F. J.: Studies of Terramycin in Premature Infants. *Pediatrics*, 12:652, 1953.
5. Deken-Grenson, M. de: Groupes des acides nucléiques intervenant dans la formation de complexes avec la streptomicine et spécificité de la réaction. *Biochim. et Biophys. Acta*, 17:157, 1955.
6. Faber, V., and Rosendal, K.: The Effect of Penicillin on the Production of Hyaluronic Acid and Hyaluronidase by Hemolytic Streptococci (Type 4, Group A). *Acta path. et microbiol. Scandinav.*, 37:286, 1955.
7. Faguet, M.: Influence du cobalt sur la multiplication de *Staphylococcus aureus* et sur l'activité antistaphylococcique de la pénicilline. *Ann. Inst. Pasteur*, 86:296, 1954.
8. Grasser, E., and Bonnas, V.: Transformations en formes L, *in vivo* de *Proteus vulgaris* sous l'action de la pénicilline. *Ann. Inst. Pasteur*, 88:651, 1955.
9. Gros, F., et al.: Recherches sur le métabolisme des amino acides. *Ann. Inst. Pasteur*, 75:446, 1949.
10. Gros, F., et al.: Mode d'action de la pénicilline chez *Staphylococcus aureus*. Inhibition d'un système enzymatique extrait des bactéries. *Compt. rend. Acad. d. sc.*, 231:184, 1950.
11. Hurwitz, C., and Rosano, C.: Role of Phosphate in Potentiating the Effect of

Dihydrostreptomycin on Culturability of *Escherichia Coli*. *Bact. Proc.*, M-51, 1955, p. 77.

12. Iyer, S. N., and others: Studies on Enzyme Inhibition in Relation to Drug Action. V. Effect of Certain Antibiotics on Liver Arginase. *J. Sci. Indust. Res.* (India), 12B: 536, 1953 (*Biol. Abst.*, 29:25536, 1955).
13. Kass, E. H., and Finland, M.: Adrenocortical Hormones in Infection and Immunity. *Ann. Rev. Microbiol.*, 7:361, 1953.

13a. Kinsell, L. W., and Jahn, J. P.: Combined hormonal-antibiotic therapy in patients with fulminating infections. *A.M.A. Arch. Int. Med.*, 96:418, 1955.

14. Latterrade-Auger, C., and Macheboeuf, M.: Influence du ribonucleate de sodium sur la croissance d'une bactérie en presence et en l'absence de pénicilline. *Ann. Inst. Pasteur*, 81:634, 1951.
15. Levadite, C.: *Le Chloramphenicol et Ses Applications Thérapeutiques*. Paris, Baillière, 1951.
16. Loomis, W. F.: On the Mechanism of Action of Aureomycin. *Science*, 111:474, 1950.
17. Macheboeuf, M., and Gros, F.: Aspects biochimiques actuels du mode d'action de la pénicilline. *J. de méd. de Bordeaux*, 130:366, 1953.
18. Michener, H. D.: The Action of Subtilin on Heated Bacterial Spores. *J. Bact.*, 70:192, 1955.
19. Newton, B. A.: Fluorescent Derivative of Polymyxin: Its Preparation and Use in Studying the Site of Action of the Antibiotic. *J. Gen. Microbiol.*, 12:226, 1955.
20. Newton, B. A.: Reversal of the Antibacterial Activity of Polymixin by Divalent Cations. *Nature*, 172:160, 1955.
21. Oginsky, E. L., and Rumbaugh, H. L.: A Cobalt-Activated Bacterial Pyrophosphatase. *J. Bact.*, 70:92, 1955.
22. Oginsky, E. L., and others: The Action of Streptomycin. IV. Fatty Acid Oxidation by *Mycobacterium Tuberculosis*, Avian Type. *J. Bact.*, 59:29, 1950.
23. Perrini, F.: L'aureomicina quale fattore di crescita nei prematuri. *Boll. Soc. ital. biol. sper.*, 27:1151, 1951.
24. Pratt, R.: Effect of Glutathione on the Response of *Escherichia Coli* to Penicillin. *J. Am. Pharm. A. (Scient. Ed.)*, 44:621, 1955.
25. Pratt, R., and Dufrenoy, J.: *Antibiotics*. 2nd ed. Philadelphia, J. B. Lippincott Company, 1953.
26. Pratt, R., and Dufrenoy, J.: Evidence for the Involvement of Glutathione in the Mechanism of Penicillin Action. *J. Am. Chem. Soc.*, 70:1671, 1948.
27. Pratt, R., and others: The Enhancement of Penicillin Effectiveness *in Vivo* by Traces of Cobalt. *J. Bact.*, 55:75, 1948.
28. Regna, P. P., and others: The Isolation and General Properties of Terramycin and Terramycin Salts. *J. Am. Chem. Soc.*, 73:4211, 1951.
29. Robinson, J. C., and others: The Effect of Oral Therapy with Cobaltous Chloride on the Blood of Patients Suffering with Suppurative Infection. *New England J. Med.*, 240:749, 1949.
30. Roche, J., et al.: Sur la signification et la prévision de l'inhibition de l'arginase par de fortes concentrations en cobalt. *Compt. rend. Soc. de Biol.*, 147:623, 1953.
31. Rosendal, K., and Faber, V.: The Effect of Penicillin on the Production of Hyaluronic Acid and Hyaluronidase by Hemolytic Streptococci (Type 28, Group A). *Acta path. et microbiol. Scandinav.*, 37:293, 1955.
32. Ross, R. T., and others: Arginine as a Factor Delaying the Infection of Chicks with *Salmonella pullorum*. *Bact. Proc.*, M-138, 1955, p. 104.
33. Saz, A. K., and others: Aureomycin-Resistant Cell-Free Nitro-reductase from Aureomycin-Resistant *Escherichia Coli*. *Bact. Proc.*, M-54, 1955, p. 78.
34. Seigneurin, R., et al.: Fixation et transport des antibiotiques par les hématiques. *Ann. Inst. Pasteur*, 89:72, 1955.
35. Smith, G. N.: Possible Modes of Action of Chloromycetin. *Bact. Rev.*, 17:19, 1953.

36. Snelling, C. E., and Johnson, R.: The Value of Aureomycin in Prevention of Cross Infection in the Hospital for Sick Children. *Canad. M.A.J.*, 66:6, 1952.
37. Šorm, F., and others: Changes in Metabolism of *Escherichia Coli* Accompanying the Development of Resistance to Chloramphenicol. *Chem. Listy*, 49:121, 1955. (In Czech: English abstract in *Chem. Abst.*, 49:12594 d, 1955.)
38. Strait, L. A., and others: Enhancement of Penicillin Effectiveness by Traces of Cobalt. *J. Am. Pharm. A. (Scient. Ed.)*, 37:133, 1948.
39. Trace, J. C., and Edds, G. T.: The Influence of Cobalt on the Action of Antibiotics. *Am. J. Vet. Research*, 15:639, 1954.
40. Umbreit, W., in *Symposium on the Mode of Action of Antibiotics*. 2nd International Biochem. Congress, Paris, 1952, pp. 63–67.
41. Umbreit, W.: Mechanisms of Antibacterial Action. *Ann. Rev. Microbiol.*, 8:167, 1954.
42. Wilson, C. O., and Gisvold, O., editors: *Textbook of Organic Medicinal and Pharmaceutical Chemistry*. 2nd ed. Philadelphia, J. B. Lippincott Company, 1954.
43. Wisseman, C. L., Jr., and others: Action of Chloramphenicol on Microorganisms. *Bact. Proc.*, 1952, p. 55.
44. Wisseman, C. L., Jr., and others: Mode of Action of Chloramphenicol. *J. Bact.*, 67:662, 674, 1954; 69: 215, 1955.
45. Zeller, E. A., and others: Studies on the Influence of Streptomycin and Other Antibiotic Agents on Some Enzymes of *Myobacterium Smegmatis*. *Proc. Staff Meet., Mayo Clin.*, 24:490, 1949.

University of California Medical Center
San Francisco 22, California (Dr. Pratt)

THE SYNTHETIC ANTIMICROBIAL AGENTS

Applied Pharmacology

HARRISON F. FLIPPIN, M.D.

GEORGE M. EISENBERG, D.SC.

Although modern antimicrobial therapy had its beginning less than a century ago, with the bacteriological discoveries of Pasteur and Koch and the prophylactic use of chemical agents for septic wounds by Lister, it was the clinical application of chemotherapeutic substances by Ehrlich which opened the gates leading to the present status of antimicrobial agents. It was Ehrlich who conceived of an antimicrobial agent as one capable of destroying the offending agent within the tissues of the body and at the same time of sufficiently low toxicity so as not to harm the host. Likewise, he emphasized that certain organisms could acquire resistance to antimicrobial agents and that the resistance of some organisms was an inherent characteristic. Although Ehrlich's dream of an ideal antimicrobial agent has not yet been fully realized, the results now being obtained with these agents in the treatment and prevention of many types of infections probably surpass Ehrlich's most optimistic expectations. This has been brought about largely as a result of two outstanding developments, namely, the synthetic antimicrobial agents, such as the sulfonamides, para-aminosalicylic acid, isoniazid and nitrofurantoin; and those products that are biosynthesized by microorganisms, the antibiotic agents. For this discussion we shall limit ourselves to the former group.

SULFONAMIDES

Historical

One of Ehrlich's notable contributions was in the field of histology with the discovery of differential staining. In the course of investigations

he observed that many of the aniline dyes possess definite antibacterial activity, but the results were disappointing, in that all the dyes he tested proved too toxic for clinical use. It remained for Domagk,[23] in 1935, to find that the aniline azodye, prontosil, is an effective chemotherapeutic agent against experimental streptococcal infections and that, contrary to Ehrlich's concept, the effectiveness of prontosil is due not to its dye moiety, but to its noncolored sulfonamide substance within the prontosil molecule. Within a relatively short period following these observations sulfanilamide and its allied compounds were unquestionably established as effective therapeutic agents against many types of bacterial infections in man.

Sulfonamide therapy proved to have definite shortcomings, however. First, many strains of bacteria are naturally resistant to their action. Second, initially susceptible strains in a species can and do develop resistance to the sulfonamide drugs during treatment, so that a number of bacterial infections are no longer amenable to sulfonamide therapy. Third, these drugs may produce a variety of serious untoward reactions, and, fourth, the antibacterial activity of the sulfonamides is diminished in the presence of pus. Because of these disadvantages, and with the introduction of the antibiotics, indications for the sulfonamides became greatly restricted. Nevertheless, within the past several years there has been a renewed interest in the use of the sulfonamides, largely as a result of the toxic reactions associated with the antibiotics.

Within a decade after the discovery of sulfanilamide, more than 5000 congeneric substances were synthesized and studied, but less than a dozen of these have attained any therapeutic importance. The more important are certain N^1-heterocyclic derivatives of sulfanilamide, namely, the sulfapyrimidines (sulfadiazine, sulfamerazine and sulfamethazine), which, by virtue of their superior antibacterial efficacy and relatively low toxicity, are generally recognized as the most satisfactory of the sulfonamides for the treatment of susceptible systemic infections. In addition, such compounds as sulfisoxazole (Gantrisin,[17] Hoffman-LaRoche), sulfadimetine (Elkosin,[52] Ciba), sulfacetamide[4] (Sulamyd, Schering) and sulfamethylthiadiazole (Thiosulfil,[5] Ayerst), because of their increased solubility and relatively higher concentration in urine, are primarily reserved for the treatment of urinary tract infections, although some of these (especially sulfisoxazole) are used in systemic infections, particularly in pediatric practice. Likewise, as a result of their poor absorption from the gastrointestinal tract, phthalylsulfathiazole[51] (Sulfathalidine, Sharp and Dohme) and succinyl sulfathiazole[51] (Sulfasuxidine, Sharp and Dohme) are used in infections of the gastrointestinal tract. Sulfanilamide, once the sulfonamide of choice, is now rarely used.

In general, there is little qualitative difference in the antimicrobic

spectrum of the various commonly used sulfonamides. The most susceptible types of organisms include streptococci, staphylococci, pneumococci, gonococci, meningococci, *Escherichia coli* and *Hemophilus influenzae*.

Chemistry and Pharmacodynamic Action

The structural formulas of the major sulfonamides are shown in Figure 1. They are all white crystalline powders and for the most part are relatively insoluble in water, but their sodium salts are readily soluble.

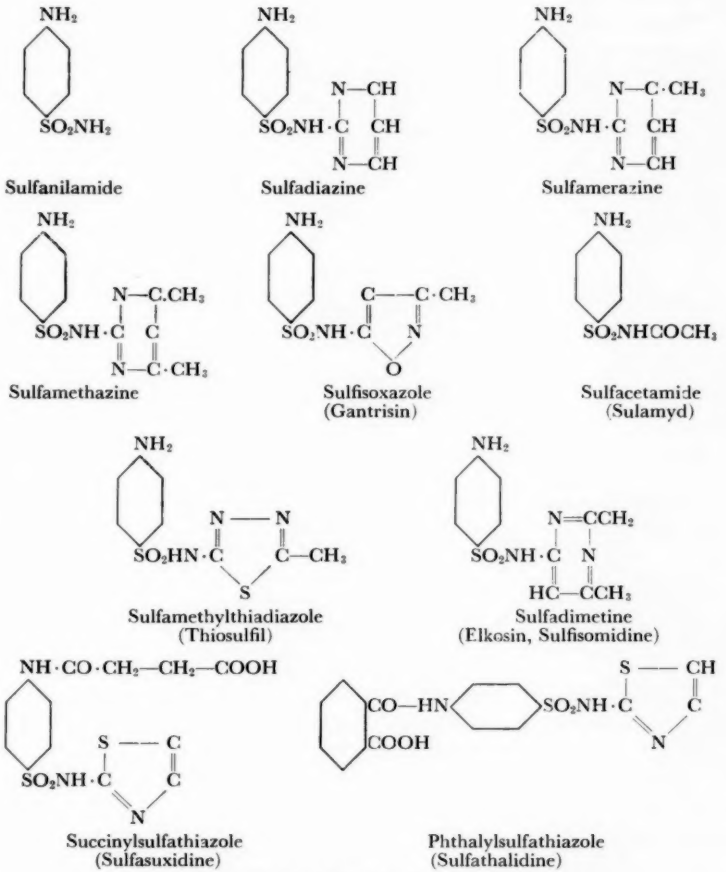


Fig. 1. Structural formulas of the major sulfonamides.

In order to know the kind of cases in which these drugs are likely to succeed, some knowledge of their mode of action is essential. At this time there are several theoretical conceptions as to the manner in which these drugs act, but no single theory has been evolved which completely explains their action. The most widely accepted theory postulates that the action of these drugs is accomplished by interference with essential metabolites by a displacement of para-aminobenzoic acid from the bacterial enzyme necessary for growth of the organism, since the bacteriostatic action of these drugs has been shown to be prevented by small amounts of para-aminobenzoic acid. With this theory it is possible to predict with reasonable accuracy the activities in vitro of new sulfonamides.

Regardless of the exact mechanism of sulfonamide activity, certain principles of treatment have evolved as a result of clinical observations of their use in several types of infections. It appears that the sulfonamides exert their greatest effectiveness in diffuse lesions, characterized by maximal tissue invasion and minimal tissue destruction. The presence of necrotic tissue or pus in a lesion prevents the compounds from acting upon the organisms with the same maximum effect which characterizes their action on diffuse, nonsuppurative infections. Furthermore, if an infection is treated after two or three days of progression, and some degree of localization or pus formation has occurred in the interim, the sulfonamides seem clinically to accomplish little more than to protect uninvolved tissue. Therefore it is important to start chemotherapy early in the disease process before pus formation takes place because, once this has occurred, the drugs are relatively ineffective.

Absorption, Distribution and Excretion

With the exception of sulfanilamide, the sulfonamides are relatively insoluble in water. However, they manifest increased solubility in body fluids. The drug concentrations reached locally and in the blood are dependent upon the rate of entry into, and exit from, the local area and the circulating blood. The rational basis for the local application of the sulfonamides is the higher concentration obtained locally, and because of the relatively greater solubility of sulfanilamide in wound fluids, its use locally has proved to be the most satisfactory. However, within recent years, this practice has been largely discontinued. When these drugs are administered by mouth, one may assume for practical purposes that all of them, with the exception of phthalylsulfathiazole and succinyl sulfathiazole, are nearly completely absorbed from the gastrointestinal tract into the blood stream within two to four hours after ingestion of moderate doses. After four to six hours the amount of drug in the circulating blood diminishes rapidly, so that it is im-

portant to administer a large initial dose, followed by smaller amounts at four to six hour intervals, in order to obtain and maintain therapeutic blood concentrations until complete clinical cures are obtained. Since irregular or varying blood concentrations have been shown to produce diminished therapeutic results, the foregoing schedule of doses should be followed if uniformly effective blood levels are to be maintained. Obviously, when these drugs are given parenterally, high blood levels are obtained more rapidly than when they are administered by mouth.

After their absorption into the blood stream the sulfonamides undergo certain chemical changes, the most important of these being the acetylation of the primary amino group, which takes place mainly in the liver. In general, approximately 20 per cent of the drug appears in the circulating blood as acetylated compound, and, since the acetyl derivatives are therapeutically inactive and tend at the same time to be more toxic, because of diminished solubility, a sulfonamide capable of a high degree of acetylation is less desirable than one with a low degree of acetylation.

For the most part, the sulfonamides resemble the behavior of urea in their uniform distribution throughout the body; they diffuse readily from the blood stream into the various body tissues and fluids, the penetration being influenced by the degree of combination with plasma proteins. The vascularity of a tissue influences its drug concentration, so that diffusion into an area of chronic infection, bone and necrotic tissue may be deficient. All these drugs are present in exudates and transudates in concentrations equal to or higher than those found in the blood. They pass readily into the cerebrospinal fluid in concentrations averaging 50 to 75 per cent of that present in the blood. Available data on sulfisoxazole, sulfacetamide and sulfadimetine indicate that these drugs traverse the hematocephalic barrier in amounts which result in lower cerebrospinal fluid concentrations than those obtained with the sulfapyrimidines.

Regardless of their route of administration, the sulfonamide drugs (with the exception of phthalylsulfathiazole and succinyl sulfathiazole) are excreted in the urine to the extent of 80 to 90 per cent of the quantity administered, both in the free and acetylated form. For the most part, this takes place within 24 to 48 hours. The percentage in the acetylated form varies with the drug and with the patient. Sulfonamide excretion is similar to that of urea, except that reabsorption by the tubules occurs to a greater extent and elimination is reduced in the presence of diminished nitrogen excretion. However, the clearance of these drugs is increased definitely by increased urinary flow rate, which can be obtained best by forcing fluids, either by mouth or, if necessary, parenterally. With a decrease in kidney function one finds an increase in drug

concentration in the blood, especially of the acetylated form. Therefore, should the urine volume become low, the possibility of stone formation in the urinary tract by crystals of the acetyl compounds, particularly sulfadiazine, sulfamerazine and sulfamethazine, is greatly increased. The possibility of such an occurrence is significantly less with sulfisoxazole, sulfacetamide and sulfadimetine, in view of the greater solubility, especially in acid urine, of the acetylated derivatives of these drugs.

Sulfonamide Mixtures

Although the belief is widely held that administration of sufficient fluid to insure high urinary output is enough to prevent crystalluria and that this hazard is the result of the low solubility of the acetylated drugs in acid urine, it has been learned that high urine volumes and the use of alkali will not forestall precipitation of sulfadiazine, sulfamerazine or sulfamethazine.[28] However, chemical and clinical studies of these agents in combination have demonstrated that the total amount of sulfonamide that can be held in solution in urine is substantially increased when two or more of these substances are administered simultaneously and that this is accomplished without sacrificing therapeutic activity.[32] Furthermore, it has been demonstrated that such a mixture is more soluble at pH 5.5 and below than any single soluble sulfonamide, such as sulfisoxazole. Hence the rationale for the combination of two or more sulfonamides as a method of decreasing renal toxicity, while maintaining antibacterial efficacy in the treatment of susceptible systemic infections.[40] For such mixtures sulfadiazine is the common denominator and is usually combined with sulfamerazine for a dual mixture, and plus sulfamethazine for a triple mixture. However, other sulfonamides, such as sulfacetamide and sulfadimetine, have been used in place of sulfamerazine in the triple combinations.

Toxicology

In discussing the untoward reactions of sulfonamide therapy, it is well to point out several factors which tend to influence their incidence and severity. The length of time that the drugs are administered and the total dose given are probably the most important factors. Children seem to tolerate these drugs better than do the aged; those with good nutrition and normal renal function better than the poorly nourished and those having kidney damage.

Mild Toxic Reactions. Ambulatory patients rather commonly complain of dizziness, especially with sulfanilamide. To recognize that dizziness may occur is important, especially in patients who operate

machines requiring precision or judgment. Cyanosis, often observed in patients receiving sulfanilamide, is less frequent and less severe with the other drugs of this group and can be disregarded. The most frequent toxic reactions are nausea and vomiting. These usually appear by the first 24 hours of therapy, but rarely become so severe as to necessitate discontinuing therapy.

Severe Toxic Reactions. In general, the incidence of the more severe toxic reactions is lower with sulfapyrimidine therapy than with other sulfonamides approaching their therapeutic effectiveness for systemic diseases.

RENAL COMPLICATIONS. The renal complications represent the most frequent and most dangerous of these toxic reactions following sulfapyrimidine administration, whereas this hazard is rarely encountered with the use of the more soluble compounds.

Two main *causes* have been established for the development of renal complications, namely, the nephrotoxic, or nonobstructive, type, the nature of which is not fully understood, but apparently has no relation to the amount of drug in the circulating blood or its concentration in the urine. Fortunately, this type is rarely encountered. The mechanical, or obstructive, type, which accounts for most of these complications from the sulfapyrimidines, is primarily caused by the intratubular deposition of poorly soluble crystals of the drug, especially the acetyl derivatives. With minor exceptions, crystalluria of the sulfapyrimidines is found only in acid urine, which is almost always the case in patients receiving these drugs without adjuvant alkali therapy. This is partially the result of restricted food intake during the febrile illness, which gives rise to a net balance of acid to be excreted by the kidneys, thereby increasing the concentration of acid in the urine. In addition, the presence of the drug itself has an acidifying effect. The solubility of the sulfapyrimidines and their acetyl derivatives in urine increases a great deal with the increasing pH within the physiologic range of urinary pH. The amounts of drug and of the acetyl derivative dissolved in a given volume of normal urine at pH 7.5 are markedly higher than the amounts dissolved at pH 5.0. Furthermore, it has been shown that the solubility of the sulfonamides is increased with a rise in the temperature of the urine.

Signs of renal involvement usually develop about the fourth day of sulfonamide therapy, but may be present as early as 24 hours after treatment has been initiated, the salient features of urinary damage following sulfonamide therapy being microscopic or gross hematuria, crystalluria, decrease in renal function, azotemia, enlargement of one or both kidneys, oliguria, anuria, and pain along the urinary tract. In some instances there occur only a small number of red blood cells in the urine and/or ureteral colic and pain in the loins or abdomen; in

others there is gross hematuria, oliguria, or anuria with increasing nitrogen retention. Although microscopic hematuria is one of the earliest signs of renal damage from these drugs, it is to be remembered that in many systemic infections, in which the drugs are not used, this finding is present. Usually, sulfonamide crystalluria is present. However, crystalluria alone does not necessarily indicate the presence of renal complications, in that approximately 25 per cent of patients receiving these drugs without adjuvant alkali therapy will show crystals in the urine. Since crystallization may take place in a cool urine, it is important to examine a freshly voided specimen which is still at body temperature.

Although the *diagnosis* of renal damage from these drugs is usually apparent, it is sometimes necessary to resort to cystoscopy to substantiate the clinical manifestations. Furthermore, ureteral catheterization enables one to determine the degree of renal impairment in each kidney, or the presence of ureteral obstruction. Not only does this maneuver serve as a diagnostic procedure, but often it also breaks up masses of crystals and serves to establish urinary drainage. Despite the fact that these uroliths are complex calcium sulfonamide compounds, they are usually devoid of sufficient calcium salts to be visualized on plain roentgenograms or retrograde pyelograms.

The *treatment* of renal complications following sulfonamide therapy may be classed as conservative, manipulative or operative. With the development of signs of kidney involvement the following conservative measures should be instituted: (1) discontinue the sulfonamide drug; (2) force fluids orally or intravenously to 4000 or 5000 cc. daily, or until signs of edema are shown; (3) administer sodium bicarbonate orally, 20 gm. in 24 hours, or, if not tolerated, administer 5 per cent sodium bicarbonate solution intravenously; and (4) diathermy over the kidneys may be of aid, since the rise in urinary temperature increases the solubility of these drugs.

If, with these conservative procedures, the urinary output is not increased to 500 cc. or more in 24 hours, or if hematuria or renal colic persists, manipulative treatment of cystoscopy and ureteral catheterization, with lavage of the renal pelvis with 5 per cent sodium bicarbonate solution, or isotonic saline solution, at a temperature of 105° F., should be carried out at once. Inlying ureteral catheters are advised for 24 hours or more, until a normal volume of urine is excreted. Early catheterization of the ureters re-establishes vital urinary drainage, restores renal function, and may prevent renal failure due to tissue damage. The inability to catheterize ureteral orifices because of ureteral block may necessitate more radical procedures, such as unilateral or bilateral nephrostomy, with or without renal decapsulation, if the oliguria or anuria persists with rise in blood nitrogen values. Decapsulation

offers the greatest and only hope of cure in cases of persistent anuria due to a calcifying nephrosis, since ureteral catheterization and pelvic lavage are of no avail.

In view of these potential renal complications following the use of the sulfapyrimidines, it is important to observe certain precautionary measures which may prevent the occurrence, or at least reduce the incidence, of these complications. Certainly a history of previous sulfonamide medication followed by toxicity is in itself a contraindication to further sulfonamide therapy. In addition, in order to augment the excretion of the drug and to avoid undue concentrations in the urine, as well as lessen the acidity, it is important to maintain the daily volume of urine in adults who receive these drugs at a minimum of 1500 cc. Since the hazard of precipitation in the urinary tract is decreased by using mixtures of partial dosage of two or three sulfapyrimidines, it is advisable to give such mixtures in the treatment of systemic infections. Furthermore, it is generally agreed that alkaline adjuvants should be used in conjunction with sulfonamide mixtures, especially when large doses of the drug are given. Although the sulfapyrimidines, singly or in combination, represent the sulfonamide of choice in the treatment of susceptible systemic diseases, in those cases in which it seems unwise to use them one may administer the more soluble sulfonamides, especially sulfisoxazole, with a wider margin of safety.

DRUG REACTIONS. Drug *fever* is seen in approximately 3 per cent of patients receiving the sulfonamides. It may occur at any time, but is most commonly seen from five to 10 days after the beginning of treatment. Frequently, drug fever may be followed by dermatitis, hemolytic anemia or neutropenia. When it occurs, treatment should be stopped. At times it is difficult to determine whether an observed temperature rise represents a drug reaction or a recrudescence of the infection. The fever of the original infection is usually normal by the third day of treatment, and if the patient is improved clinically, one should suspect that the rise in temperature is due to the drug. The leukocyte count may or may not be elevated during drug fever. As a rule, if the drug is causing the fever, the temperature will drop within 24 to 48 hours following cessation of therapy while fluids are forced.

Drug *rashes* occur with the sulfonamides in approximately 2 per cent of patients and may occur at any time after the beginning of treatment, especially after the fifth day. If the patient's condition warrants, the drug may be continued with caution, although it is best to stop treatment. Psychoses due to these drugs occur at any time. If the infectious process is under control when psychosis is observed, the drug is best discontinued.

OTHER REACTIONS. Depression of the white blood cells may occur at any time, but most cases of agranulocytosis have occurred after 12 days

of treatment. Acute hemolytic anemia, seen chiefly following sulfanilamide, may occur following the use of any of the sulfonamides. When it appears, usually during the first four days of treatment, the drug should be stopped immediately. Mild anemia of the hemolytic type is seen more frequently, but does not constitute a serious problem. Other toxic effects, such as hepatitis, nephritis, myocarditis, purpura haemorrhagica and neuritis, may be seen. In addition to these immediate toxic reactions, there has been a great deal of interest regarding the possibility that these drugs may give rise to changes in the blood vessels simulating periarteritis nodosa.

Methods of Administration and Dosages

The sulfonamide compounds are administered locally, orally and parenterally. The local use of these drugs has been for the most part disappointing, although they are still being used in certain specialties. In general, their administration by mouth constitutes the most satisfactory method. However, in certain instances when a rapid elevation of the drug concentration in the blood is desired, or when oral medication is impractical or impossible, it is necessary to resort to parenteral administration. Sulfanilamide, because of its relatively high solubility in water, can be given subcutaneously or intravenously, as a 1 per cent solution in sterile physiologic saline solution. Best results with sulfanilamide are obtained via the subcutaneous route. For intravenous therapy with the sulfapyrimidines (sulfadiazine, sulfamerazine and sulfamethiazine) a 5 per cent solution of the sodium salt in sterile distilled water is preferred. Parenteral preparations are likewise available for certain of the more soluble compounds.

Several factors influence the amount of drug required to produce the desired result. As a rule, the dosages are smaller when the compounds are used prophylactically than when they are used therapeutically. Patients treated in bed usually are given larger amounts than those who are ambulatory. The type of infecting organism must be considered for its susceptibility to the drug and also whether the infection is mild or severe. Acute conditions, involving soft tissues, require different dosages than do chronic bone or urinary tract infections. Moreover, certain factors, such as kidney function, drug absorption and the state of dehydration, all tend to influence the amount of drug found in the blood. From this it becomes apparent that it is impossible to outline a course of sulfonamide therapy which will suit the needs of every patient. Therefore the following recommendations on dosage are for the treatment of adult patients suffering with acute infections severe enough to warrant full sulfonamide dosage. For infants and children the dose schedule is proportioned as to weight and age.

For sulfanilamide a blood concentration of free drug of 10 mg. per 100 ml. will give maximum therapeutic effectiveness in most types of infections caused by susceptible organisms. Blood concentrations at this level can be attained by an initial dose of 3 to 5 gm. of sulfanilamide by mouth followed by doses of 1.0 to 1.3 gm. every four hours day and night until the temperature has been normal for 72 hours, along with signs of clinical improvement. The dose then is reduced gradually until complete cure is obtained. This dose schedule may be applied in general to the parenteral administration by the subcutaneous route, although the rate of absorption by the tissues will influence the same. In general, it is necessary to give the drug every six to eight hours in order to maintain adequate blood levels of free drug. The dosage of the sulfapyrimidines (sulfadiazine, sulfamerazine and sulfamethazine) is essentially the same, and, although the amount of free drug in the blood is of doubtful significance, a concentration above 5 mg. per 100 ml. should give maximum results. In meningitis higher concentrations, about 15 mg. per 100 ml., are desirable. Sulfadiazine is preferred in this instance, in that somewhat higher cerebrospinal fluid levels are attained. The usual dosage by mouth for these drugs consists of an initial dose of 3 to 4 gm., followed by 1 gm. every four to six hours, day and night.

Likewise, the same dose schedule is observed with the various sulfonamide mixtures, the accepted ratios of the sulfonamide combinations being 1:1:1 for triple and 1:1 for dual mixtures. For intravenous use with the sodium salt, the dosage is calculated on the basis of 0.006 gm. per kilogram of body weight and is repeated at six-hour intervals. For the most part the dose schedule for the more soluble sulfonamides is somewhat larger than for the sulfapyrimidines, in that the blood levels are more sustained with the former. However, urine concentrations of the latter group are much greater; hence their usefulness in the treatment of urinary tract infections. For the relatively nonabsorbable sulfonamides (phthalylsulfathiazole and succinyl sulfathiazole), the usual dose is 2 gm. every four to six hours orally.

Indications

At this time the sulfonamides are indicated in the treatment of uncomplicated urinary tract infections, bacillary dysentery and meningococcal infections, also chancroid and trachoma, and are used in combination with the antibiotics in certain other types of infections, such as pneumonia, meningitis and actinomycosis. Furthermore, such drugs as phthalylsulfathiazole and succinyl sulfathiazole, which are poorly absorbed and are largely excreted in the feces, are used prophylactically in the preparation of large bowel surgery.

Contraindications

The only possible contraindication to sulfonamide treatment is a history of a previous sensitivity to sulfanilamide and its derivatives as manifested by drug fever, gross hematuria, dermatitis, hemolytic anemia, neutropenia or jaundice. Certainly in patients with such a history one should select some other form of therapy, such as the antibiotics, rather than run the risk of continuing sulfonamide toxicity. In ambulatory patients receiving the sulfonamides it is best to advise against the use of alcohol, as at times they tend to cause marked dizziness. Aside from this, there seems to be no evidence that any other form of medication or food is contraindicated.

PARA-AMINOSALICYLIC ACID

Historical

In 1940–41 Bernheim[6] observed that oxygen consumption of tubercle bacilli is increased in the presence of benzoic or salicylic acid. He postulated that these or closely related compounds participate in the normal metabolism of the tubercle bacillus and suggested the possibility that chemical analogues might have a reverse effect. Lehmann[38] confirmed the stimulatory activity of these aromatic acids upon oxidative metabolism, but, more important, he noted that this property was associated with an inhibitory effect upon the growth and reproduction of virulent tubercle bacilli. Similar inhibitory activity, in the absence of demonstrable oxidative metabolic changes, was shown to occur in a bovine strain of *Microbacterium tuberculosis*. In a subsequent investigation of the structure-activity relationship of derivatives of benzoic and salicylic acids, he showed that para-aminosalicylic acid (PAS) is the most active of the many compounds studied.[39] Demonstration of activity in vivo in the experimental animal was followed by clinical trials which eventually showed that PAS, when used alone in the treatment of tuberculosis, is inferior to streptomycin, despite its remarkable performance in vitro. This inferiority was attributed to (*a*) the necessity of continuously giving large doses, and (*b*) comparatively rapid development of resistance of tubercle bacilli to the drug. Nevertheless, PAS has greatly increased the usefulness of streptomycin and isoniazid, so that today it is the most important auxiliary drug in our antituberculous armamentarium. When given concomitantly with either or both of the latter drugs, it significantly retards the emergence of resistant tubercle bacilli.

Chemistry and Pharmacodynamic Action

The structural formula of PAS is shown in Figure 2. The pure compound is soluble in water to the extent of about 0.2 per cent. Aqueous

solutions are unstable and give rise to meta-aminophenol by decarboxylation. The sodium salt of PAS is considerably more soluble in water, and the resulting solutions, neutral or slightly alkaline, are relatively stable. The preparation, physical and chemical properties of PAS and its salts are discussed in detail by Bogen, Loomis and Will.[9]

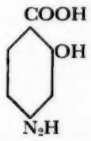


Fig. 2. Structural formula of para-aminosalicylic acid.

The presence of the amino group in PAS profoundly alters the systemic activity of PAS, despite the close chemical kinship of the compound to salicylic acid. Unlike the latter, PAS has no effect on the respiratory center and does not produce the syndrome of salicylism; it has neither analgesic nor antipyretic activity.

Absorption and Excretion

Para-aminosalicylic acid is rapidly absorbed from the gastrointestinal tract, the rate of absorption depending in part upon the physical form of the drug administered and whether the free acid or sodium salt is used. Granules or compressed, enteric-coated PAS tablets are more slowly absorbed than are solutions of the sodium salt. Blood levels following oral administration of PAS are lower and persist for shorter periods of time than is the case when the sodium salt is administered.[26] After a single oral dose of 4 gm. of the acid, maximum blood concentrations ranging from 3 to 12 mg. per 100 ml. are achieved within 90 to 120 minutes; equivalent dosage of the sodium salt produces similar concentrations, but in less time. After administration of single oral doses, blood PAS concentrations rapidly decline (three to five hours), so that the drug must be administered frequently in order to maintain continuous levels.

Upon absorption, PAS diffuses freely through the tissues, reaching concentrations in the pleural fluid and other body fluids approaching or equalling those encountered in the blood. Most investigators agree that little, if any, PAS can be detected in the cerebrospinal fluid or exudate after oral administration of the usual dosages.

In the occasional patient in whom oral use of PAS is contraindicated or not feasible, the sodium salt of PAS may be administered intravenously; however, the material is generally too irritating for subcutaneous, intramuscular or intraspinal administration. The intravenous use

of a combination of sodium para-aminosalicylate and polyvinyl pyrrolidone, by Weiss, Seven and Eisenberg,[67] has shown the possibility of establishing PAS blood concentrations about twice as high as those which could be demonstrated in the same patients when these were given equivalent amounts of sodium PAS alone. In addition, therapeutic blood concentrations were maintained twice as long, and significant cerebrospinal concentrations were also demonstrated. However, this combination is not available commercially.

Most of the PAS is excreted in the urine, between 80 and 85 per cent being recoverable in the urine within 10 hours of administration. Part is recovered as free PAS acid and part as the sodium salt. Approximately 50 per cent of the amount recovered occurs in the acetylated form, as acetyl-aminosalicylic. Free and acetylated para-aminosalicyluric acid and 2.4-dihydroxybenzoic acid have also been reported as occurring.[66] Neither meta-aminophenol nor glycuronamide has been found as a degradation product in vivo. The rapid excretion of PAS results in high urinary concentration (400 to 900 mg. per 100 cc.), and in view of the insolubility of the free acid and acetylated PAS, alkalinization of urine is desirable. The use of sodium para-aminosalicylate is felt to reduce the probability of crystalluria to a negligible factor.

Para-aminosalicylic acid excretion is retarded in the presence of renal insufficiency. Probenecid, p-(Di-n-propylsulfanyl)-benzoic acid, has been reported effective in decreasing renal excretion of PAS and thereby contributing to the development of blood PAS concentrations several fold greater than those attainable without it.[10]

Dosage, Route of Administration and Clinical Toxicity

Para-aminosalicylic acid is administered orally in doses varying from 8 to 16 gm. per day. The usual dose is 12 gm. of acid, or 15 gm. of the sodium salt. This total daily dose is usually given in four equal portions in order to maintain relatively constant blood concentrations.

It is probable that much of the divergent opinion regarding PAS toxicity reported soon after the introduction of the drug into clinical usage was due to associated impurities. More recently there has been general agreement that the direct toxic effects of PAS are principally confined to the gastrointestinal tract and are manifested symptomatically as nausea, vomiting, diarrhea and abdominal distress. Opinions regarding the relation between dosage and severity of these symptoms are at variance; doses as low as 8 gm. per day have been reported as producing toxic effects. On the other hand, three times this dose are reported to have been used without complaint.

Like salicylic acid, PAS slightly depresses prothrombin formation in the liver; however, it should be borne in mind that the blood-clotting

mechanism is affected by many factors, including alcoholism and poor nutrition. In any event, the decrease in blood prothrombin content does not appear to be of clinical importance.

Hypokalemia has been described as a toxic manifestation of PAS therapy.[14] More recently, evidence has been presented to suggest that the observed hypokalemia is in large measure secondary to gastrointestinal disturbances, specifically vomiting and diarrhea.[44] This conclusion appears to have merit in view of the demonstration that patients receiving the potassium salt of para-aminosalicylic acid may show lowered serum potassium concentrations.[15]

Other troublesome side reactions have been reported. A partial list includes (1) skin rashes of various types;[64, 65] (2) drug fever;[21] (3) hay fever-like syndrome;[65] (4) allergic pneumonitis;[2, 61] (5) leukopenia, atypical lymphocytosis and aplastic anemia;[49, 63] (6) symptom complex simulating tuberculous meningitis;[12] (7) Guillain-Barré syndrome.[13]

Despite the variety of these untoward reactions, the frequency with which they have been encountered is remarkably low, considering the number of patients to whom the drug has been administered. In a series of 1734 courses of treatment, of which 1061 consisted of streptomycin and either PAS or sodium para-aminosalicylate, slightly more than 2 per cent had to be discontinued because of toxic reactions, one-half of these being because of allergic reactions.[59] It can, therefore, be said that with PAS reactions are fortunately few.

ISONIAZID

Historical

The discovery of isoniazid (INH), one of the most effective antituberculous drugs known at present, was somewhat fortuitous. In 1945 Chorine[19] reported that nicotinamide possesses tuberculostatic activity, an observation confirmed several years later by McKenzie and his associates.[46] Comparative activity studies of numerous compounds structurally related to nicotinamide revealed that many of these, including derivatives of isonicotinic acid, are tuberculostatic. About this time considerable interest was being evinced in the thiosemicarbazones, and in the course of attempts to synthesize the thiosemicarbazone of isonicotinylaldehyde, isonicotinylhydrazine (isoniazid) was isolated as an intermediate and its potent antituberculous activity demonstrated.[29] After the initial reports of the successful treatment of tuberculosis in human beings with INH,[25, 26] rapid clinical evaluation in large groups of patients offered a more realistic appraisal of the therapeutic possibilities of the drug than was originally disseminated by publicity in the lay press. These studies showed that while INH is a potent antituberculous agent, it is not as effective when used alone as it is when used in com-

bination with either para-aminosalicylic acid or streptomycin, a conclusion based on the degree of roentgenologic improvement or sputum conversion. Further, tubercle bacilli appeared to develop resistance to isoniazid more rapidly when the drug was administered alone than when it was used in combination. There is little doubt that INH is at least equal, and in some respects superior, to streptomycin in the chemotherapy of tuberculosis.

Chemistry and Pharmacodynamic Action

The structural formulas of isoniazid and several closely related compounds are shown in Figure 3.

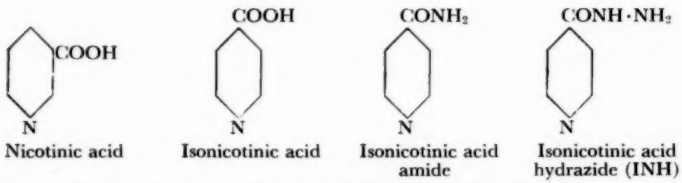


Fig. 3. Structural formulas of isoniazid and several closely related compounds.

Isoniazid is a white, crystalline powder, highly soluble in water. It has been found that the hydrazide group is necessary for activity, although aliphatic or simple aromatic hydrazides are devoid of activity.[7]

Pharmacodynamic effects with isoniazid appear only when excessive doses are administered. The paucity of such effects when the usual therapeutic dose is given has been emphasized by Benson, Stefko and Roe.[5] Intestinal activity has not been observed to be altered; salivation and lacrimation were not suppressed. The drug has no direct antipyretic effect and produces no significant change in blood pressure. Similar lack of effect upon respiration, blood pressure and cardiac function has been reported by others.[27, 58]

Absorption, Distribution and Excretion

Isoniazid is readily absorbed from the gastrointestinal tract. After a single oral dose of 3 mg. per kilogram in man, maximum concentrations, in the range of 1 to 3 micrograms per milliliter, are attained in the plasma between one and six hours after ingestion.[25] These concentrations are estimated to be 20 to 80 times the inhibitory dose in vitro. Drug concentrations of 0.4 microgram per milliliter or higher persist in plasma for six to 24 hours after administration. Isoniazid gains access to many body fluids and organs, including cerebrospinal fluid, saliva, feces, lung and pleural cavity. Definitive investigations of the

absorption, distribution and excretion of INH have been reported by several groups of investigators,[4, 57] using isotopic C^{14}-labeled INH, who found that after intramuscular injections to tuberculous patients peak plasma concentrations were established in an hour. Though these concentrations fell off rapidly during the ensuing eight hours, measurable quantities of drug were detectable in blood and plasma for three to seven days thereafter. It was also shown that, in addition to diffusion into the lungs and skin, isoniazid easily gained access into dense, caseous lesions in the lungs and lymph nodes, persisting in high concentrations for several hours. Excretion was mainly by the kidneys, small amounts occurring in the feces and eliminated by the lungs as carbon dioxide. In general, these findings corroborate those of earlier investigators using conventional procedures.

Unlike streptomycin, isoniazid has been shown to be equally active against intracellular and extracellular tubercle bacilli.[45] Radioactive tracer studies designed to clarify the mode of action of isoniazid against tubercle bacilli indicate a delayed effect on susceptible bacilli in contrast to a more immediate effect produced by streptomycin.[3] This would suggest that isoniazid produces a bacteriostatic activity by interfering with the formation of some essential metabolite. The favorable distribution of INH in the body, its ability to penetrate into and persist in tissues particularly vulnerable to invasion by tubercle bacilli, and its high activity against intracellular organisms combine to make this drug a valuable antituberculous agent.

Dosage and Administration

Experience has shown that the usual effective dose of INH is 3 to 5 mg. per kilogram of body weight, given orally in two or three divided doses per day. A daily dose of 7 to 10 mg. per kilogram may be used in the treatment of tuberculous meningitis, miliary tuberculosis or in seriously ill patients. Isoniazid should always be administered concomitantly with either streptomycin or PAS, or both.

Clinical Toxicity

The toxic manifestations of isoniazid are many, though they occur infrequently and few are of such great importance as to require cessation of therapy. Available data suggest that incidence of untoward reactions to isoniazid is related to dose. At a dosage level of 3 mg. per kilogram per day the incidence has been estimated to be 1 per cent, but rises sharply to 15 per cent at dose ranges of 10 mg. per kilogram per day. More recently it has been estimated that toxicity occurs in 5 per cent of patients receiving 150 to 300 mg. per day, and that in

1 per cent the severity of the untoward reaction is such as to necessitate discontinuing the drug.[54]

The chief side reactions are related to the central nervous system, the commonest symptoms being twitching of muscles, restlessness, insomnia and headache; hyperreflexia can often be demonstrated. In many instances these reactions disappear upon withdrawal of the drug and frequently even if it is continued. Rarely are they important enough to interfere with therapy. An occasional patient may manifest subtle personality changes manifested as irritability or euphoria, but these are difficult to evaluate. Much more important, but fortunately less common, toxic manifestations are peripheral neuritis, difficulty in micturition, toxic psychoses and acute convulsive reactions, the latter two more frequently seen in patients with organic brain damage.[35, 41, 47, 53] Pyridoxine deficiency has been reported with high doses of INH;[8] administration of pyridoxine[42] and vitamin B_{12} has been reported efficacious in relieving peripheral neuritis.[1]

The allergic reactions to isoniazid are of infrequent occurrence. They include chills, fever, dermatitis, arthralgia, purpura and hemolytic anemias.

In summary, it can be said that the introduction of isoniazid provides a most potent drug for the treatment of tuberculosis and provides the clinician with a choice of therapeutic regimens.

NITROFURANTOIN

Historical

In 1944 Dodd and Stillman[22] found that the addition of a 5-nitro group to the furan ring conferred significant antibacterial activity on the derivative. Subsequently, nitrofurazone[20] (Furacin, Eaton) was developed, and clinical experience has shown it to be beneficial in the topical treatment of infected superficial sites.[11, 43] More recently, nitrofurantoin, N-(5-nitro-furfurylidene)-1-aminohydantoin (Furadantin, Eaton), has been shown to be effective in vitro against gram-positive and gram-negative bacteria (except Pseudomonas), but ineffective against fungi and viruses.[48, 50, 62] A number of clinical investigations have been reported on the use of the drug in the treatment of urinary tract infections.[30, 31, 34, 37, 48, 50, 55, 60, 62]

Chemistry and Pharmacodynamic Action

The structural formula of nitrofurantoin is shown in Figure 4. Nitrofurantoin is a yellow, crystalline compound, soluble in water or urine

at room temperature to the extent of about 20 mg. per 100 cc.[48] At pH 7.5 to 7.7 solubility is increased to approximately 230 mg. per 100 cc. It has been stated that nitrofurantoin can exist in urine in a state of stable supersaturation. This is attributed to the observation that when large amounts of the drug are dissolved in urine in vitro at pH 7.5, reduction of the pH to 5.5 does not produce precipitation.[48] The

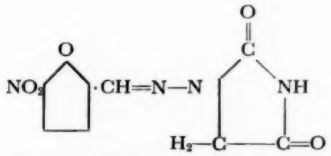


Fig. 4. Structural formula of nitrofurantoin (Furadantin).

writers are unable to find any reports specifically describing the pharmacodynamic effects of nitrofurantoin.

Absorption and Excretion

Nitrofurantoin is rapidly absorbed from the gastrointestinal tract. Information on blood concentrations, though meagre, is conflicting. Carroll and Brennan,[16] using a spectrophotometric method of assay, report average blood concentrations of 2.23 mg. of nitrofurantoin per liter in patients receiving doses of 5 to 7 mg. per kilogram or 500 to 600 mg. daily. Peak levels were observed two hours after ingestion of the drug. In a patient with impaired renal function higher blood levels were not observed. In contrast, other investigators,[53] using a twofold tube dilution bio-assay technique with a strain of *Escherichia coli* inhibited by 0.8 mg. per 100 ml. of nitrofurantoin, were unable to detect any antibacterial activity in the serum or plasma of patients after 200-mg. doses of nitrofurantoin. It would thus appear that if nitrofurantoin is absorbed into the blood at all, only minimal, biologically inactive amounts can be demonstrated when clinically effective doses (5 to 10 mg. per kilogram per day) are used.

Preliminary studies reveal that approximately 40 per cent of nitrofurantoin administered to man is excreted in the urine, negligible amounts occur in the feces, while the remainder is apparently catabolized into inactive, brownish compounds that may tint the urine. Excretion occurs in eight hours, the larger portion being eliminated within four hours. Urinary concentrations in the range of 25 to 50 mg. per 100 cc. have been reported occurring four to six hours after maximal clinical doses.[18, 55]

Clinical Toxicity

On the basis of information currently available, nitrofurantoin appears to be a drug of low toxicity. With oral administration in an average daily dose of 5 to 8 mg. per kilogram (2.2 to 3.6 mg. per pound) of body weight in divided doses four times daily, nausea and emesis are encountered in an occasional patient. These side effects can frequently be prevented or minimized by administering the drug with each meal and with food at bedtime, or by reducing the dosage.

Proctitis, anal pruritus, crystalluria, abdominal pain and disturbance of the normal ecologic distribution of fecal flora have not been observed in one group of 79 patients receiving nitrofurantoin for 14 days.[48] In four patients who received the drug prior to demise, no toxic effects on the testicles, kidney, liver or ovaries were found.[62] In a study of 100 patients[34] no evidence of adverse effects on erythropoiesis or liver function attributable to nitrofurantoin was apparent. Severe nausea and vomiting, necessitating withdrawal of the drug or decrease in dosage, occurred in about 5 per cent of cases. Headache was encountered in 3 per cent, dizziness in 6 per cent, and urticaria in 1 per cent. In two patients in whom no obvious neurologic disease or condition was present prior to administration of nitrofurantoin, numbness of an extremity was noted after one week of therapy. This disappeared when the drug was withdrawn and recurred in one instance with reinstitution of the drug. Cutaneous and febrile reactions suggesting the development of hypersensitivity to the drug have been described.[24, 34, 36, 60] It would thus seem that within the limits of the information available at present, nitrofurantoin appears to be a relatively safe and effective urinary antiseptic.

SUMMARY

The chemical treatment of bacterial disease was reopened with the discovery of the effectiveness of the sulfonamides against a variety of infections. Likewise, the dramatic results obtained with penicillin reawakened interest in the biosynthetic products of microorganisms as anti-infective agents. These two developments constitute the basis of modern antimicrobial therapy. Although the antibiotics alone are effective in combating many types of infectious processes, there are others in which the synthetic antimicrobial agents are indicated, alone or in combination with the antibiotics. At this time we have reviewed briefly the present status of the more commonly used chemical agents, namely, the sulfonamides, para-aminosalicylic acid, isoniazid and nitrofurantoin.

REFERENCES

1. American Trudeau Society, Report of the Committee on Therapy: The Current Status of Isoniazid in the Treatment of Tuberculosis. *Am. Rev. Tuberc.*, 67: 269, 1953.
2. Atwell, R. J., and Prior, J. A.: Allergic Pneumonitis during Chemotherapy for Tuberculosis: Report of Two Cases Due to PAS. *Ann. Int. Med.*, 42:190, 1955.
3. Barclay, W. R., Ebert, R. H., and Koch-Weser, D.: Mode of Action of Isoniazid. *Am. Rev. Tuberc.*, 67:490, 1953.
4. Barclay, W. R., Ebert, R. H., LeRoy, G. V., Manthei, R. W., and Roth, L. J.: Distribution and Excretion of Radioactive Isoniazid in Tuberculosis Patients. *J.A.M.A.*, 151:1384, 1953.
5. Benson, W. M., Stefko, P. L., and Roe, M. D.: Pharmacologic and Toxicologic Observations on Hydrazine Derivatives of Isonicotinic Acid (Rimifon and Marsilid). *Am. Rev. Tuberc.*, 65:376, 1952.
6. Bernheim, F.: Effect of Various Substances on Oxygen Uptake of Tubercle Bacillus. *J. Bact.*, 41:387, 1941.
7. Bernstein, J., Lott, W. A., Steinburg, B. A., and Yale, H. L.: The Chemotherapy of Experimental Tuberculosis. *Am. Rev. Tuberc.*, 65:357, 1952.
8. Biehl, J. P., and Vilter.: Effects of Isoniazid on Pyridoxine Metabolism. *Tr. 13th Conf. on Chemotherapy of Tuberculosis*, 1954, p. 237.
9. Bogen, E., Loomis, R. N., and Will, D. W.: Para-aminosalicylic Acid Treatment of Tuberculosis: A Review. *Am. Rev. Tuberc.*, 61:226, 1950.
10. Boger, W. P., and Pitts, F. W.: Influence of p-(Di-n-propylsulfinyl)-Benzoic Acid, "Benemid," on Para-aminosalicylic Acid (PAS) Plasma Concentration. *Am. Rev. Tuberc.*, 61:862, 1950.
11. Brennan, J. W.: The Use of Furacin in Ophthalmology. *Am. J. Ophth.*, 35: 1343, 1952.
12. Bridge, E. V., and Hofmann, G. N.: Reaction to Para-aminosalicylic Acid Simulating Tuberculous Meningitis. *Am. Rev. Tuberc.*, 64:682, 1951.
13. Bulley, K. G.: Near Fatal Shock from PAS Followed by Guillain-Barré Syndrome. *Am. Rev. Tuberc.*, 69:455, 1954.
14. Caley, F. E. de W.: Potassium Deficiency in p-Aminosalicylic Acid Therapy. *Lancet*, 1:447, 1950.
15. Campbell, A. H., and Neufeld, O. E.: The Cause of Hypokalemia Following PAS Therapy. *M. J. Australia*, 1:725, 1951.
16. Carroll, G., and Brennan, R. V.: Furadantin. *J. Urol.*, 71:650, 1950.
17. Carroll, G., Allen, H. N., and Flynn, H.: Gantrisin in the Treatment of Urinary Infections. *J.A.M.A.*, 142:85, 1950.
18. Carroll, G., Brennan, R. V., and Jacques, R.: Furadantin: Human Blood Level and Urinary Excretion. *South. M. J.*, 48:149, 1955.
19. Chorine, V.: Action de l'amide nicotinique sur les bacilles du gendre Mycobacterium. *Compt. rend. Acad. d. sc.*, 220:150, 1945.
20. Daily, L. E.: The Nitrofurans. *New York State J. Med.*, 48:1386, 1948.
21. Daven, J. R., and Rogers, A. E. T.: Febrile Reactions to Para-aminosalicylic Acid. *Am. Rev. Tuberc.*, 61:643, 1950.
22. Dodd, M. C., and Stillman, W. B.: In Vitro Bacteriostatic Action of Some Single Furan Derivatives. *J. Pharmacol. & Exper. Therap.*, 82:11, 1944.
23. Domagk, G.: Ein Beitrag Chemotherapie der bakteriellen Infektionen. *Deutsche med. Wchnschr.*, 61:250, 1935.
24. Draper, J. W., Zufall, R., Rosenberg, L. T., and Knight, V.: Effect of Nitrofurantoin on Bacteruria of Infections Following Prostatic Operation. *J. Urol.*, 72:1211, 1954.
25. Elmendorf, D. F., Jr., Cawthon, W. W., Muschenheim, C., and McDermott, W.: The Absorption, Distribution, Excretion, and Short-Term Toxicity of Isonicotinic Acid Hydrazide (Hydrazid) in Man. *Am. Rev. Tuberc.*, 65:429, 1952.

26. Fisher, B. M., Roberts, G., and Henshaw, H. C.: The Subcutaneous Administration of the Salt of Para-aminosalicylic Acid in the Treatment of Tuberculosis. *Am. Rev. Tuberc.*, 64:557, 1951.
27. Fisher, M. M., and others: Isonicotinic Acid Hydrazide and Its Derivatives in Tuberculosis: An Evaluation of the Side Effects in Relation to Peripheral Circulation. *New York State J. Med.*, 52:1519, 1952.
28. Flippin, H. F., and Reinhold, J. G.: An Evaluation of Sulfonamide Mixtures and Various Adjuvants for Control of Sulfonamide Crystalluria. *Ann. Int. Med.*, 25:433, 1946.
29. Fox, H. H.: Synthetic Tuberculostats. III. Isonicotinaldehyde Thiosemicarbazone and Some Related Compounds. *J. Org. Chem.*, 17:555, 1952.
30. Friedgood, C. E., and Ripstein, C. B.: Furadantin in Treatment of Infections Due to B. Proteus. *Bull. New York Acad. Med.*, 30:322, 1954.
31. Friedgood, C. E., and Ripstein, C. B.: Furandantin in Treatment of Infections Due to Antibiotic-Resistant Organisms. *Internat. Rec. M. & G. P. Clin.*, 167:218, 1954.
32. Frisk, A. R., Hagerman, G., and Helender, S.: "Sulfacombination"—A New Chemotherapeutic Principle. *Brit. M.J.*, 1:7, 1947.
33. Goodhope, C. D.: Thiosulfil in Urinary Tract Infections. *Tr. West. Sect., Am. Urol. A.*, 49–53, August, 1954.
34. Hasen, H. B., and Moore, T. D.: Nitrofurantoin, A Study in Vitro and in Vivo in 100 Cases of Urinary Infection. *J.A.M.A.*, 155:1470, 1954.
35. Hughes, H. B., Biehl, J. P., Jones, A. P., and Schmidt, L. H.: Metabolism of Isoniazid in Man as Related to the Occurrence of Peripheral Neuritis. *Am. Rev. Tuberc.*, 70:266, 1954.
36. Jensen, H. B., Lund, J., and Poulson, P. E.: Furadantin in Chemotherapy of Urinary Tract Infections. *Ugesk laeger*, 116:53, 1954.
37. Johnson, S. H., and Marshall, M.: Nitrofurantoin Therapy of Urinary Tract Infections in Children. *A.M.A. Am. J. Dis. Child.*, 89:199, 1955.
38. Lehmann, I.: Para-aminosalicylic Acid in the Treatment of Tuberculosis; Preliminary Communication. *Lancet*, 1:15, 1946.
39. Lehmann, I.: Effect of Isomers of PAS (Para-aminosalicylic Acid) and Related Substances on Tuberculostatic Effect of PAS. *Experientia*, 5:365, 1949.
40. Lehr, D.: Comparative Merits of Gantrisin and a Sulfapyrimidine Triple Mixture. *Antibiotics & Chemother.*, 3:71, 1953.
41. Liebing, H. N.: Peripheral Neuropathy in Tuberculous Patients Treated with Isoniazid. *Am. Rev. Tuberc.*, 68:458, 1953.
42. Lonfield, A. N., and Middleton, J. W.: B_{12} in the Treatment of Peripheral Neuritis Due to Isoniazid. *Tr. 13th Conf. on Chemotherapy of Tuberculosis*, 1954, p. 239.
43. McCullough, N. C.: Treatment of Infected War Wounds with a Nitrofuran. *Indust. Med.*, 16:128, 1947.
44. McIntyre, P. A.: Hypokalemia Occurring during PAS Therapy. *Bull. Johns Hopkins Hosp.*, 92:210, 1953.
45. Mackeness, G. B., and Smith, N.: Action of Isoniazid (Isonicotinic Acid Hydrazide) on Intracellular Tubercle Bacilli. *Am. Rev. Tuberc.*, 66:125, 1952.
46. McKenzie, D., Malone, L., Kushner, S., Oleson, J. J., and SubbaRow, Y.: The Effect of Nicotinic Acid Amide on Experimental Tuberculosis of White Mice. *J. Lab. & Clin. Med.*, 33:1249, 1948.
47. Mellon, E. W., Wright, K. W., and Bunn, P. A.: The Long Term Toxicity of Metabolic Effects of Isoniazid in Adults. *Am. Rev. Tuberc.*, 67:652, 1953.
48. Mentzer, S., Kadison, E. R., Shlaes, W. H., and Felsenfeld, O.: Treatment of Urinary Tract Infections with a New Antibacterial Nitrofuran. *Antibiotics & Chemother.*, 3:151, 1953.
49. Mulette, S. J., and Agress, H.: Toxic Reactions to Para-aminosalicylic Acid and Isoniazid Accompanied by Leukopenia and Atypical Lymphocytosis. *Am. Rev. Tuberc.*, 69:824, 1954.

50. Norfleet, C. M., Jr., Beamer, P. R., and Carpenter, H. M.: Furadantin in Infections of the Genito-Urinary Tract. *Southeast. Sect., Am. Urol. A.*, 1952, p. 26.
51. Poth, E. J.: Intestinal Antisepsis in Surgery. *J.A.M.A.*, 153:1516, 1953.
52. Prior, J. A., and Saslow, S.: Observations on Absorption, Distribution, and Excretion of Elkosin in Man. *J. Lab. & Clin. Med.*, 38:420, 1951.
53. Reilly, R. H., and others: Convulsant Effects of Isoniazid. *J.A.M.A.*, 152:1317, 1953.
54. Report to Council on Pharmacy and Chemistry, A.M.A.: Chemotherapy of Tuberculosis in Man. *J.A.M.A.*, 154:52, 1954.
55. Richards, W. A., Riss, E., Kess, E. H., and Finland, M.: Nitrofurantoin, Clinical and Laboratory Studies in Urinary Tract Infections. *A.M.A. Arch. Int. Med.*, 96:437, 1955.
56. Robitzek, E. H., Selikoff, I. J., and Ornstein, G. G.: Chemotherapy of Human Tuberculosis with Hydrazine Derivatives of Isonicotinic Acid. *Quart. Bull. Sea View Hosp.*, 13:27, 1952.
57. Roth, L. J., and Manthei, R. W.: Distribution of C^{14} Labeled Isonicotinic Acid Hydrazide in Normal Mice. *Proc. Soc. Exper. Biol. & Med.*, 81:566, 1952.
58. Rubin, B., and Burke, J. C.: Further Observations on the Pharmacology of Isoniazid. *Am. Rev. Tuberc.*, 67:644, 1953.
59. Schwartz, W. S., and Moyer, R. E.: The Incidence of Severe Toxic Reactions to Streptomycin and Para-aminosalicylic Acid. *Tr. 11th Conf. on Chemotherapy of Tuberculosis*, 1952, p. 197.
60. Trafton, H. M., Beutner, E. H., Petronio, J. J., Lind, H. E., and Correia-Branco, M.: Furadantin in Urinary Tract Infections. *New England J. Med.*, 252:383, 1955.
61. Tuckman, H.: Löffler's Reaction to Para-aminosalicylic Acid. *Am. Rev. Tuberc.*, 70:176, 1954.
62. Waisbien, B. A., and Crowley, W.: Nitrofurantoin, Clinical and Laboratory Evaluation. *A.M.A. Arch. Int. Med.*, 95:653, 1955.
63. Walters, H. A.: Aplastic Anemia Following the Use of Streptomycin and Para-aminosalicylic Acid. *Am. Rev. Tuberc.*, 68:455, 1953.
64. Warring, F. C., Jr., and Howlett, K. S., Jr.: Allergic Reactions to PAS. *Tr. 11th Conf. on Chemotherapy of Tuberculosis*, 1952, p. 192.
65. Warring, F. C., Jr., and Howlett, K. S., Jr.: Allergic Reactions to Para-Aminosalicylic Acid. Report of Seven Cases, Including One Case of Loeffler's Syndrome. *Am. Rev. Tuberc.*, 65:235, 1952.
66. Way, E. L., Smith, P. K., Howie, D. L., Weiss, R., and Swanson, R.: Absorption, Distribution, Excretion, and Fate of PAS. *J. Pharmacol. & Exper. Therap.*, 93:368, 1948.
67. Weiss, W., Seven, M., and Eisenberg, G. M.: The Intravenous Use of a Combination of Sodium Para-Aminosalicylate and Polyvinyl Pyrrolidone in the Chemotherapy of Tuberculosis. *Am. J. M. Sc.*, 225:560, 1953.
68. Welebir, F., and Barnes, R. W.: The Use of Sulfacetamide in Bacillary Infections of the Urinary Tract. *J.A.M.A.*, 117:2132, 1941.

255 South 17th Street
Philadelphia 3, Pa. (Dr. Flippin)

PENICILLIN

Applied Pharmacology

SYDNEY ROSS, M.D.

In spite of the advent of several other antibiotics within recent years, penicillin still remains the most widely used antibacterial agent in pediatrics, and in many bacterial infections it continues to be the drug of choice.

Several definite advantages account for its continuing popularity. These might be catalogued as follows: (1) low toxicity; (2) bactericidal effect; (3) advent of semisynthetic compounds such as procaine penicillin and benzathine penicillin, which have the virtue of slow absorption from the injection site; (4) less expense in comparison with other antibiotics—a 300,000-unit intramuscular dose of procaine penicillin costs less than five cents.

There are a few manifest disadvantages to penicillin, however, which make it less than the perfect antibiotic. Briefly, these would include the following: (1) limited antimicrobial spectral range—penicillin exerts little if any antibacterial activity against gram-negative bacilli; (2) resistance of strains of bacteria—this applies chiefly to the increasing number of penicillin-resistant *Staphylococcus aureus* strains; (3) resistance to penicillinase; (4) allergenicity; (5) relatively poor absorption after oral ingestion; (6) rapid excretion by the kidney; (7) poor penetration into the cerebrospinal fluid and across membranous barriers.

In spite of these shortcomings, penicillin continues to reign as the prince of antibiotics, with little likelihood that its position will be usurped in the near or distant future.

In the following discussion some of the applied pharmacologic aspects of penicillin in pediatrics will be considered, together with a summary of the present clinical indications for the drug.

SOURCE

Currently, the notatum-chrysogenum group of penicillia are the highest yielding strains and are used almost exclusively in the commercial production of penicillin. The observation that corn-steep liquor enhances the yield of penicillin manyfold has been largely contributory in accelerating production of the drug. The rich content of phenylalanine in corn-steep liquor is responsible for the latter. Production of penicillin from the mold constitutes the only method of producing large amounts of the drug, since synthetic methods have never been practical.

PHYSICAL AND CHEMICAL PROPERTIES

Chemistry

Figure 5 shows the molecular structure of all the penicillins. As will be noted, the formula is characterized by a common nucleus, and

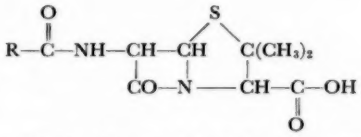


Fig. 5. Structural formula of penicillin.

the only difference to be observed is in the nature of the side chain (R). Attention is directed to the fact that the penicillin nucleus is the chief requirement for antimicrobial activity.

Several semisynthetic penicillins have been produced, these compounds differing only in the side chain. The antibacterial activity of these semisynthetic penicillins is quite similar to that of the natural penicillins and is enumerated as follows:

Penicillin O. This semisynthetic penicillin is obtained by growing the mold in a medium containing allyl-mercaptoacetic acid. It resembles penicillin G closely except that it may be less prone to produce allergenic reactions.

Procaine Penicillin G. Procaine penicillin G is obtained by the interaction of penicillin G and procaine. It is the most important and widely used repository penicillin preparation available today.

Benzathine Penicillin G (Bicillin or Permapen). Benzathine penicillin G is produced by a combination of one mol of N,N-dibenzylethylene diamine with 2 mols of penicillin G. This form of penicillin has considerable virtue as a long-acting repository preparation.

Penicillin V. Penicillin V, a recent addition to the semisynthetic

penicillins, is obtained by replacing the benzyl radical of penicillin G with the phenoxymethyl radical. Because of the latter, penicillin V is highly insoluble in the acid medium of the stomach and passes through into the duodenum virtually unchanged. This produces higher blood levels than might be obtained with comparable doses of penicillin G.

Solubility

Both the sodium and potassium salts of penicillin are very soluble in water. On the other hand, the procaine salt of penicillin is only minimally soluble in water (0.4 per cent), while benzathine penicillin is even less soluble than procaine penicillin (0.02 per cent).

Unitage

The sodium salt of penicillin provides the standard of reference: one unit of penicillin activity equals 0.6 microgram of penicillin G. Thus 1 mg. of pure sodium penicillin G is the equivalent of 1667 units of penicillin activity.

Effect of Tissue Constituents on Penicillin

The antibacterial activity of penicillin is not impaired to any degree by tissue constituents, since there is no inhibition exerted by blood, pus or tissue autolysates. This is in marked contrast to the sulfonamides. Serum albumin forms an inactive protein complex with penicillin with 60 per cent of plasma penicillin G protein-bound. The degree of protein binding is not sufficient to neutralize the activity in vivo of penicillin G, provided the plasma levels of the drug are two to five times higher than the concentration necessary to inhibit the same organism in vitro.

ABSORPTION

Penicillin absorption is predicated on the mode of administration. The following briefly summarizes pertinent data on absorption of the drug.

Oral Administration

Penicillin G. Only about one fourth of penicillin G is absorbed from the gastrointestinal tract, since there is partial destruction by gastric acidity. After passing through the stomach, penicillin G is absorbed rapidly from the duodenum, maximum blood levels being achieved

within 30 to 60 minutes after ingestion.[19, 20] Oral penicillin is preferably taken on an empty stomach about a half-hour before the next meal. Oral doses should be four to five times the intramuscular dose to produce comparable blood levels.[5]

Benzathine Penicillin. Benzathine penicillin may be administered orally with production of satisfactory blood levels. It is less influenced by concomitant food ingestion and appears to be resistant to destruction or inactivation in the gastrointestinal tract. Hence benzathine penicillin may be given without regard to meals. It is stable in aqueous suspension (unlike penicillin G) and requires no refrigeration. When a dose of 13,000 units per kilogram of body weight was administered to children, Coriell et al.[6] observed blood levels of 0.195, 0.137 and 0.083 unit per milliliter after one, two and three hours respectively. These levels were well above the maximum penicillin resistance of beta hemolytic streptococci, which is usually 0.03 unit per milliliter.

Penicillin V. This form of penicillin is stable in acid media because of the phenoxymethyl radical. Hence gastric destruction is regarded as minimal, and the drug passes through the stomach with negligible inactivation.

Intramuscular Administration

Aqueous Crystalline Penicillin. With intramuscular aqueous crystalline penicillin, peak levels are achieved within 15 to 20 minutes after injection. Hildick-Smith et al.[11] showed that optimal bactericidal levels (0.1 to 0.4 unit per milliliter) were obtained with a daily dose of 5000 units per pound given every three hours, or 10,000 units per pound every six to eight hours. Aqueous crystalline penicillin is largely reserved in current day pediatric practice for severely ill children with diseases such as meningitis, septicemia, osteomyelitis, mastoiditis, and so forth. Thus it represents primarily a hospital item and is infrequently used in office pediatric practice since the advent of the repository forms of penicillin.

Procaine Penicillin G. Procaine penicillin G has the virtue of slow absorption from the injection site. Peak plasma levels are considerably below those obtained with aqueous crystalline penicillin. Effective blood concentrations are reached within one to three hours after a single dose. Hildick-Smith et al.[11] gave procaine penicillin intramuscularly to a series of children in doses of 6000 units per pound, producing optimal bactericidal levels for 24 hours or more after a single injection. The average blood concentration at the end of 24 hours was 0.5 unit per milliliter.

Benzathine Penicillin. Single injections of 1.2 million units of benzathine penicillin in children will result in demonstrable blood con-

centrations for periods up to four weeks.[22] Even though the serum concentrations of penicillin are low, they are adequate in infections caused by susceptible organisms such as beta hemolytic streptococci.

Since the advent of procaine aqueous penicillin and benzathine penicillin, other repository forms of penicillin have been largely discarded. There are definite objections in the pediatric age group to the use of other delaying agents containing sensitizing oil bases such as sesame oil, beeswax or aluminum monostearate.

TISSUE DISTRIBUTION

Eagle et al. have demonstrated the desirability of large and intermittent dosage of penicillin and the need for producing blood concentrations which are many times the minimum inhibitory concentration in vitro.[9] These investigators have also shown unequivocally the necessity for prolonged therapy in order effectively to eradicate foci of infection containing large numbers of organisms.[10] The tissue level of penicillin effective at a focus of infection is probably the same as the level effective in vitro. The bactericidal effect of penicillin in vivo against certain species of bacteria stops abruptly as soon as the plasma penicillin content falls to ineffective levels.

Intermittent intramuscular injections of aqueous crystalline penicillin are preferable to repository penicillin preparations for the eradication of deep and walled-off foci of infection.[9] The lower concentrations in the blood and tissue fluids after repository penicillin administration make it less likely that a sufficient concentration of penicillin can be brought to bear in the tissues to inhibit the causative organism. However, in instances in which the organism is sufficiently sensitive, as in beta hemolytic streptococcal infections, and when there is adequate transport of penicillin to tissue fluids, repository preparations may well suffice.

Penicillin is widely distributed throughout the body after systemic administration, but concentrations vary substantially in different tissues and body fluids. Only small amounts of penicillin enter the cerebrospinal fluid when the meninges are normal in view of the size of the penicillin molecule, which prevents ready transport across the blood-brain barrier. When the meninges are acutely inflamed, penicillin may penetrate into the cerebrospinal fluid, resulting in therapeutic concentrations. However, there is considerable variation and lack of dependability unless, as Dowling et al. have shown, aqueous penicillin is given in massive doses in the order of one million units every two hours.[7] A dose of this magnitude will assure adequate cerebrospinal fluid concentrations.

After therapeutic doses of the drug minimal penicillin concentrations

are present in brain tissue, joint spaces, and pericardial and pleural fluids, while slightly higher levels appear in peritoneal fluid. Low concentrations are present in skeletal and cardiac muscle, pancreas, spleen and adrenal gland. On the other hand, sizable concentrations appear in the blood, bile, skin, intestine and liver, and extremely high concentrations are present in the kidney.

Penicillin is rapidly excreted by the kidney, accounting for the prompt disappearance of the drug from the serum within two to four hours after a therapeutic dose of the aqueous crystalline preparation. The use of repository forms of the drug or the concomitant administration of probenecid, which blocks tubular excretion, provides for a longer duration of therapeutic serum penicillin concentrations. Renal clearance values are considerably lower in very small infants because of incomplete development of kidney function; as a result, after dosage proportionate to body surface area, the persistence of penicillin in the blood is several times as great in premature infants as in children and adults.[3]

TOXICITY AND SIDE EFFECTS

Reactions to penicillin are rare in the pediatric age group even when massive doses are given.

Local tissue irritation at the site of parenteral injections characterized by pain and induration is not infrequent, but generally is inconsequential. Occasionally peripheral nerve injury may occur, but is usually transitory. Benzathine penicillin is considerably more irritating than procaine penicillin after intramuscular injection, especially when large doses are given.

Cutaneous skin eruptions such as urticaria, morbilliform eruptions and atopic dermatitis are the most frequent allergic manifestations of penicillin. These dermatitides may occur irrespective of the mode of administration of the drug, although hypersensitivity reactions are considerably less frequent with oral than parenteral penicillin. Penicillin sensitization may occur seven to 10 days after exposure to the drug, presenting a clinical picture closely akin to that of serum sickness; these symptoms include painful swollen joints, urticaria, fever, muscle pains and lymphadenopathy. Topical application of penicillin has resulted in a high incidence of sensitization and has been largely abandoned in favor of bacitracin, which is as effective locally as penicillin and has a low incidence of sensitization. Similarly, penicillin lozenges have no place in pediatric therapy.

Penicillin sensitization in children may occur after initial exposure or may manifest itself at the time of subsequent administration of the drug.

The majority of allergic eruptions are controlled by discontinuation of penicillin and administration of antihistamines and/or epinephrine. The more severe reactions may be singularly benefited by the use of corticoids.

For optimum prevention of penicillin anaphylaxis, the drug should not be given for trivial conditions. Before it is administered to a child, the mother should be questioned about allergic status, previous use of penicillin and any unusual reaction to the antibiotic. Diagnostic skin and conjunctival tests to determine in advance the possibility of penicillin sensitivity are both impractical and unreliable.

Hypoallergenic penicillin preparations such as penicillin O and 1-ephenamine penicillin G (Compenamine) have been developed recently. These are supposed to have a lower hypersensitivity index than penicillin G. However, there has been little critical evaluation of the virtues of these semisynthetic forms in the pediatric age group.

Parenthetically, the question frequently arises whether allergic children are more liable to sensitization to penicillin than are nonallergic children. In an attempt to answer this problem, Berkowitz et al.[4] gave penicillin to 411 children, of whom 280 were known to be allergic. Of the latter, 10 per cent had allergic reactions to the drug, whereas in the 131 nonallergic children no hypersensitivity reactions were observed. This would suggest that the administration of penicillin to allergic children carries with it a greater possibility of sensitization than in nonallergic children. However, Levin and Moss[16] in a similar controlled experiment concluded that a pre-existing allergy in the child does not predispose to penicillin hypersensitivity. These investigators[16] offer an interesting possible explanation to account for the low incidence of penicillin sensitivity in children as compared with adults. They suggest that this is due in part to the relative infrequency of fungus sensitivity in younger persons and that the activity and duration of fungus infections are important in mediating such sensitivity and may account for the much greater incidence of penicillin sensitivity in adults.

It should be borne in mind that, in large doses, oral penicillin may occasionally produce gastrointestinal disturbances similar to those encountered with other antibiotics such as the tetracyclines.

DOSAGE AND ROUTES OF ADMINISTRATION

There is currently a plethora of penicillin preparations available to the physician. A confusing situation arises from the fact that a host of pharmaceutical firms attach their own names to the drug as a means of commercial identification. This multiplicity of products may indeed be likened to the welter of vitamin preparations on the market bearing names garbled beyond all recognition. It would be wise for

the pediatrician to concern himself with only a few preparations of penicillin with which he may familiarize himself and confine himself to these.

The choice of penicillin regimens depends on the nature of the infection, type of organism, and convenience and comfort to the patient. The following methods of administration are available.

Oral Penicillin

Generally speaking, for the average mild illness in the pediatric age group, oral penicillin may be used.[5, 19, 20] It has the virtue of simplicity and convenience and is less likely to produce hypersensitivity reactions than parenteral penicillin. It is advisable not to rely on oral penicillin

TABLE 1. *Dosage Forms of Penicillin in Pediatrics*

FORM OF PENICILLIN	MAINTENANCE DOSE	DOSAGE INTERVAL
Oral penicillin G	Under 30 lbs., 25,000 units/lb./24 hrs. Over 30 lbs., 600,000 units/day	Every 4–6 hrs. Give ½ hr. before meals or 2 hrs. after meals
Oral benzathine penicillin (Bicillin or Permapen)	300,000–1.2 million units/day orally	4–8 hrs.
Crystalline aqueous penicillin (sodium or potassium salt)	Under 30 lbs., 10,000 units/lb./24 hrs. IM Over 30 lbs., 300,000–600,000 units/24 hrs.	Every 3 hrs.
Procaine aqueous penicillin G	Under 30 lbs., 10,000 units/lb./24 hrs. IM Over 30 lbs., 300,000–600,000 units/24 hrs.	One injection every 24 hrs.
Benzathine penicillin IM (Bicillin or Permapen)	600,000–1.2 million units IM	Usually given as a single dose IM, or may repeat in a few days

in severe infections such as meningitis, septicemia, osteomyelitis, and so forth. Oral penicillin is useful for tapering off therapy after intramuscular penicillin has been given.

Oral penicillin may be used in the treatment of the average case of pneumococcal pneumonia and streptococcal infections in view of the marked sensitivity to penicillin of these two organisms. Similarly, oral penicillin is widely used currently in rheumatic fever prophylaxis.[14]

The three chief variants of oral penicillin include penicillin G, benzathine penicillin and penicillin V.

A recommended oral dosage schedule is indicated in Table 1.

Parenteral Penicillin

There are few children in the average pediatric practice who have not, in their short worldly sojourn, been on the receiving end of a "shot of penicillin." The ensuing struggle is generally of such intensity that the pediatrician dreads the occasion as much as the child does. However, when a child is moderately or severely ill, it is much the better part of discretion to invoke the parenteral route rather than rely on the less predictable oral administration of the drug.

The three parenteral forms in most common use today include crystalline aqueous penicillin G, procaine penicillin G and benzathine penicillin.

Crystalline Aqueous Penicillin G. Rapidly absorbed aqueous crystalline penicillin should be administered for highly resistant organisms or for organisms relatively inaccessible in body cavities or abscesses. This form of the drug can be given intramuscularly, intravenously or into body cavities. The sodium or potassium salts are most frequently used. It is stable in the dry form up to three years. Solutions buffered to pH 6 retain full potency for one week in the refrigerator. After intramuscular injection the highest penicillin serum concentration is usually achieved within one-half hour with a moderately rapid tapering off so that at the end of three hours either suboptimal levels or no demonstrable penicillin is observed in the blood. Dosage intervals range from three to six hours in the pediatric age group. The total daily dose of aqueous crystalline penicillin is given in Table 1.

Crystalline penicillin may be instilled intrathecally in a concentration not to exceed 1000 units per milliliter. Not over 5000 to 10,000 units of the drug should be administered daily intrathecally in the pediatric age group. As previously noted, there is currently little need for intrathecal penicillin in pyogenic meningitis therapy when massive doses (1,000,000 units every two to three hours) are given intramuscularly.[7]

Procaine Aqueous Penicillin G. Repository penicillins are particularly advantageous in the treatment of children in the home or office. Procaine penicillin is currently far and away the most commonly used form of the drug in pediatrics. Because of its prolonged action, only one injection a day is required. It has become common practice among pediatricians to give aqueous procaine penicillin in a dose of 300,000 units daily irrespective of the age or weight of the child. This is essentially an adult dose. However, there is only a desultory attempt on the part of physicians to base penicillin dosage on body weight in pedi-

atrics. This is predicated on the fact that excessive amounts of penicillin are not accompanied by toxic manifestations and also that the drug is so inexpensive. This is not the case, however, with broad-spectrum antibiotics or sulfonamides. A 300,000-unit dose of procaine penicillin contains 120 mg. of procaine. This amount of procaine is rarely toxic because it is in the form of a poorly soluble salt and hence is only slowly absorbed. Procaine penicillin should never be injected intravenously or into body cavities.

Benzathine Penicillin (Bicillin or Permapen). This long-acting repository penicillin in a dose of 1.2 million units intramuscularly produces blood levels greater than 0.05 unit per milliliter for about one month in children. This concentration, although low, would suffice in hemolytic streptococcal infections. It is generally conceded, however, that benzathine penicillin finds its greatest usefulness in prophylaxis rather than in the treatment of an acute infection. Stollerman and Rusoff[22] have reported excellent results in prophylaxis against group A streptococci in patients with rheumatic fever.

Table 1 summarizes the maintenance dose and dosage interval of penicillin in pediatrics. These dosage recommendations are at best only rough approximations, since it should be borne in mind that a knowledge of the specificity and severity of the infection, sensitivity of the organism to penicillin and an evaluation of the clinical course of the child are more important criteria for dosage than any arbitrary schedule.

GENERAL COMMENTS ON CURRENT PENICILLIN THERAPY

The Problem of Penicillin-Resistant Staphylococci

There has been a definite increase in the number of penicillin-resistant *Staphylococcus aureus* strains. Most of the data thus far reported concern hospital patients and do not necessarily reflect a similar high incidence in the general public. Resistant staphylococci are commonly found in the nares and skin of nurses and physicians in the hospital and are in all probability transmitted by cross infection from hospital attendant to patient and from one patient to another. Ludlam[17] has reported that 100 per cent of newborn infants acquired resistant staphylococci after one to 10 days in the nursery; after release of the infants from the hospital their resistant flora was lost, so that by the time they were one year old only 8.7 per cent were still carriers. Needham and Nichols[18] at Mayo Clinic reported 10 per cent carriers of resistant staphylococci in outpatients, while Dowling et al.[8] gave figures of 18 per cent carriers of penicillin-resistant strains for the public

as a whole. This is in sharp contrast to the 60 to 80 per cent resistant staphylococci found in hospital populations.

Thus the problem of penicillin-resistant staphylococci is more a hospital problem than one that is indigenous to the community at large. However, it is still an acute problem which may become more serious in spite of alternative antibiotics available for therapy. The potential gravity of the situation has in part been alleviated by the discovery of new antibiotics such as erythromycin, cathomycin, vancomycin and amimycin, which may be successfully used in the treatment of resistant staphylococcal infections. Chloramphenicol has also enjoyed considerable vogue as a useful antibiotic in such infections in view of the relative rarity (approximately 6 per cent) of chloramphenicol-resistant staphylococci.[21] On the other hand, the tetracyclines are sharing with penicillin an increasing incidence of resistant staphylococci in hospital populations. At the present writing approximately 45 to 55 per cent of staphylococci isolated from hospitalized infants and children are resistant to oxytetracycline, chlortetracycline and tetracycline.[21]

Penicillin Resistance of Organisms Other than Staphylococci

In spite of extended use of penicillin for approximately 15 years, there has fortunately been no change in the clinical efficacy of this drug against infections caused by group A beta hemolytic streptococci, pneumococci, gonococci or treponema. Sensitivities in vitro among recently isolated strains of these species show no decreasing penicillin activity. The oft-expressed fear that, as with the sulfonamides, widespread use of penicillin would result in increased resistance of many bacterial species has indeed been shown to be without basis in fact. Thus the only bona fide situation in which penicillin resistance poses any real problem remains the staphylococci. This is important to bear in mind and provides the rationale for the claim that penicillin remains the drug of choice in the majority of gram-positive coccal infections in spite of the advent of broad-spectrum antibiotics and erythromycin.

The Problem of Antagonism between Penicillin and the Broad-Spectrum Antibiotics

Much has been written regarding the antagonism between bactericidal antimicrobial agents (such as penicillin and streptomycin) and bacteriostatic drugs (such as the tetracyclines and chloramphenicol). The experimental observations of Jawetz et al. indicated that chlortetracycline, oxytetracycline and chloramphenicol are at times capable of interfering with the action of both penicillin and strepto-

mycin.[12, 13] Lepper and Dowling[15] have added a clinical counterpart to these experimental observations in their report of 14 patients with pneumococcal meningitis treated with both penicillin and chlortetracycline, of whom 11 died, whereas in a control group treated with penicillin alone, only three cases ended fatally. However, there is little additional clinical evidence to support Jawetz's experimental observations on antagonism. Ahern and Kirby[2] treated 25 cases of pneumococcal pneumonia with a combination of chlortetracycline and penicillin and observed much the same clinical response as in a comparable control group of 25 patients treated with penicillin alone. Similarly, Walker[23] found no interference between chloramphenicol and penicillin in the treatment of acute streptococcal pharyngitis. Ahern, Burnell and Kirby[1] found in an experimental streptococcal infection of mice that chloramphenicol inhibited the bactericidal action of penicillin only if both drugs were given in a single injection. If effective levels of the antibiotic were sustained for a period of days, no antagonism was observed. Thus clinical antagonism between penicillin and the broad-spectrum antibiotics is virtually precluded. One should have no compunction regarding the simultaneous use of penicillin and one of the broad-spectrum antibiotics in any given patient.

Weight vs. Unitage for Expressing Penicillin Dosage

It would be preferable to use weight (milligrams) rather than units to express potency of penicillin preparations even though the unit system is currently used almost exclusively. Not only is weight a more precise expression, but also it avoids misleading comparisons; e.g., one million units of penicillin sounds like a tremendous dose, whereas it is comparable to only 600 mg. of other antibiotics. An intramuscular dose of 300,000 units represents only 190 mg. of penicillin.

Effect of Massive Doses of Penicillin

High doses of penicillin are still accompanied by a low degree of toxicity, differing in this regard from other antibiotics and sulfonamides. Thus doses up to 100 million units of potassium penicillin G have been given in refractory cases of subacute bacterial endocarditis without untoward reactions.

The Indiscriminate Use of Penicillin in Pediatric Practice

One gets the impression (without any clear-cut statistical proof) that penicillin and other antibiotic agents are perhaps used more indiscriminately in children than in any other group of patients. The

reason is understandable, even though one cannot necessarily condone the practice. The most common infection seen in pediatrics is the upper respiratory infection. The incidence of respiratory complications such as otitis media, cervical adenitis, bronchitis and pneumonia is inordinately high, especially in infants and young children. The pediatrician or general practitioner, seeing a child at home or in the office with an upper respiratory infection, is not likely to perform any bacteriologic laboratory studies to determine the inciting bacterial agent. Nor is a white blood cell count frequently invoked as a diagnostic aid. These studies would be routine with a hospitalized child, but the vast majority of children receiving penicillin or other antibiotics are treated outside the hospital. Thus the physician, seeing the child on a house or office visit, must make a quick decision, based entirely on clinical findings, whether to give an antibiotic or withhold it. A clinical estimate of whether or not a respiratory infection is due to a bacterial agent which will respond to antibiotics, or a viral agent which will not, is at best only a rough guess. Thus the temptation is strong to give antibiotics in any such equivocal situation so as "not to take any chances." This practice of giving antibiotics when in doubt is further intensified by the overt or covert pressure on the part of the parents to give the child "a shot of penicillin" or prescribe one of the new "wonder drugs." Any physician doing pediatric practice can attest to the oppressive proportions which this latter consideration can at times assume.

These are some of the factors which perhaps account for the *excessive* use of penicillin and other antibiotics in the pediatric age group. I would perhaps prefer to use the term *excessive* rather than *indiscriminate*, since the latter has a somewhat sterile connotation in view of the difficulties inherent in a situation in which only clinical indices are available to help decide whether an antibiotic is being used with or without adequate reason. In brief, one must probably accept the premise that the discriminating use of antibiotics is frequently predicated on adequate laboratory facilities and that the latter are not generally used except in the hospitalized patient. This does not preclude intelligent use of antibiotics in the home or in the office, but admittedly makes it somewhat more difficult when only clinical criteria are available. The rapid defervescence of fever in a self-limited virus respiratory infection is frequently accepted a priori by both physician and parent alike as the direct therapeutic result of a "shot of penicillin" given the day before.

INDICATIONS

Tables 2 and 3 attempt to present a concise survey of the penicillin-susceptible infections commonly encountered in infants and children,

TABLE 2. *Therapeutic Indications for Penicillin in Pediatrics*

TYPE OF INFECTION	DRUG OF CHOICE	COMMENT
Staphylococcal: Acute osteomyelitis	Penicillin Erythromycin Chloramphenicol Tetracyclines	In all staphylococcal infections sensitivity of organism should be determined promptly. If organism is penicillin-sensitive, give 500,000 units aqueous crystalline penicillin every 4–6 hrs. IM for 1 week, then 600,000 units procaine aqueous penicillin IM twice daily for 3–5 weeks. Surgery necessary only in presence of large soft tissue abscesses. Danger of relapse if penicillin discontinued too soon. Recoveries approach 85%. Erythromycin or chloramphenicol alternative treatment if organism is penicillin-resistant
Chronic osteomyelitis	Penicillin Erythromycin Chloramphenicol Tetracyclines	Results not too satisfactory. Sequestrectomy necessary. Maintain penicillin therapy for 3–6 weeks. Additional local administration of penicillin (500 units/ml.) postoperatively
Furunculosis, cellulitis and soft tissue abscess	Penicillin Erythromycin Chloramphenicol Tetracyclines	Procaine aqueous penicillin 300,000 units IM initially, followed by oral penicillin for 4–7 days. Surgical drainage of pus if necessary. Erythromycin (10 mg./lb./24 hrs.) good alternative therapy.
Meningitis	Penicillin Erythromycin Chloramphenicol Tetracyclines	Prompt determination of sensitivity of organism important. Intensive therapy indicated. Give 1,000,000 units crystalline aqueous penicillin IM every 3 hrs. for 4–6 days; then continue with procaine aqueous penicillin (600,000 units twice daily) for another 7–10 days. No intrathecal penicillin necessary. If organism is penicillin-resistant, chloramphenicol and erythromycin good alternative therapy
Pneumonia	Penicillin Erythromycin Chloramphenicol Tetracyclines	Difficult to determine when causative organism of pneumonia is *Staphylococcus aureus* unless it is isolated from blood culture or empyema fluid. Give 600,000 units procaine aqueous penicillin daily IM; maintain therapy for approximately 7 days after temperature normal. When empyema is present, instill 50,000 units of penicillin daily into pleural space (1 ml. = 2000 units). If no improvement, thoracotomy necessary. Erythromycin or broad-spectrum antibiotics also effective
Cutaneous infections, including impetigo and pyoderma	Systemic: Penicillin or Erythromycin Local: Bacitracin or erythromycin ointment	Penicillin or erythromycin orally usually produces rapid recovery. Topical bacitracin or erythromycin ointment efficacious in milder cases. Broad-spectrum antibiotics may also be used

TABLE 2. *Therapeutic Indications for Penicillin in Pediatrics (Continued)*

TYPE OF INFECTION	DRUG OF CHOICE	COMMENT
Streptococcal: Upper respiratory infections, including pharyngitis and tonsillitis	Penicillin Tetracyclines Erythromycin Sulfadiazine	Penicillin is drug of choice in group A beta hemolytic streptococcal infections. Streptococci (group A) markedly susceptible to penicillin (0.03 unit/ml.), with penicillin-resistant strains rare. Oral penicillin yields good results. Continue penicillin therapy for 5-10 days to eradicate beta hemolytic streptococci from nasopharynx. Benzathine penicillin (1.2 million units IM as a single dose) may also be used. Rheumatic fever extremely rare when strep. throat properly treated with penicillin. Tetracyclines and erythromycin alternative therapy. Sulfadiazine less effective in eradicating beta hemolytic streptococci from oropharynx
Otitis media	Penicillin and sulfadiazine combination Broad-spectrum antibiotics	Otitis media best treated with combination of penicillin and sulfonamides. Procaine aqueous penicillin IM initially (600,000 units) followed by sulfonamides (triple sulfas) for 7 days usually adequate and precludes likelihood of relapses. Myringotomy rarely indicated
Mastoiditis	Penicillin and sulfadiazine combination Broad-spectrum antibiotics	Intensive penicillin and sulfonamide therapy required to eradicate focus and prevent relapses. Crystalline aqueous penicillin 500,000 units IM every 4 hours for 3–4 days; then switch to procaine aqueous penicillin IM (600,000 units twice daily) for one week; then taper off with oral penicillin for 2 more weeks. Concomitantly give triple sulfas (1 grain/lb./24 hrs.) for 10–14 days. Mastoidectomy rarely indicated
Scarlet fever	Penicillin Tetracyclines Erythromycin Chloramphenicol Sulfonamides	Procaine penicillin (300,000 units IM daily) or oral penicillin (800,000 units daily) for 7–10 days. Benzathine penicillin (1.2 million units IM as a single dose) also provides good therapeutic results. Any of above regimens will reduce incidence of complications and result in negative throat cultures (usually within 4–7 days). Broad-spectrum antibiotics and erythromycin also effective. Antitoxin rarely necessary
Subacute bacterial endocarditis	Penicillin Broad-spectrum antibiotics Streptomycin	Sensitivity of organism should be ascertained before therapy initiated. Approximately 600,000–900,000 units penicillin IM daily for about 1 month. Higher doses necessary if relapses occur. Periodic penicillin assays should be done. If blood culture remains positive, a combination of penicillin and streptomycin should be used. Four to 6 months' follow-up indicated

TABLE 2. *Therapeutic Indications for Penicillin in Pediatrics (Continued)*

TYPE OF INFECTION	DRUG OF CHOICE	COMMENT
Pneumococcal:		
Pneumonia	Penicillin Broad-spectrum antibiotics Erythromycin Sulfonamides	Pneumococci very sensitive to penicillin, which remains drug of choice. Procaine aqueous penicillin 300,000 units IM daily for 4–5 days adequate in most cases. Oral penicillin 800,000 units per day also yields satisfactory results. Tetracyclines, chloramphenicol and erythromycin also effective in pneumococcal pneumonia
Meningitis	Penicillin and sulfadiazine combined Broad-spectrum antibiotics Erythromycin	Pneumococcal meningitis still a formidable disease requiring intensive therapy. Crystalline aqueous penicillin (1,000,000 units every 3 hrs. IM) and sulfadiazine (2–3 grains/lb./24 hrs.). No intrathecal therapy necessary. May substitute procaine penicillin for crystalline aqueous penicillin after 4–5 days. Continue therapy until temperature is normal and cerebrospinal fluid sterile for 10 days. Broad-spectrum antibiotics have also been used successfully. May expect 80–90 per cent recovery if infection is treated early and energetically
Gonococcal:		
Ophthalmia of the newborn	Penicillin Broad-spectrum antibiotics	Aqueous crystalline penicillin 50,000 units IM every 8 hrs. for 3 days usually adequate. Penicillin ophthalmic ointment topically is advisable. Broad-spectrum antibiotic may also be given
Vulvovaginitis, urethritis	Penicillin Broad-spectrum antibiotics	Procaine penicillin 300,000 units IM daily for 3 days curative in 95% of cases. Oral penicillin also effective in dosage of 800,000 units daily for 3 days. Criteria of cure—3 negative cultures over 21 day follow-up. If Herxheimer reaction elicitated during therapy, suspect coexistent syphilis. Broad-spectrum antibiotics also effective when treatment is continued for 4–5 days
Meningococcal:		
Meningococcemia or meningitis	Sulfadiazine Penicillin Broad-spectrum antibiotics	Excellent results with sulfadiazine alone with 95% recovery. Give 2–3 grains/lb./24 hrs. and continue for 7 days after temperature is normal and cerebrospinal fluid sterile. Penicillin as supplementary therapy recomended. Broad-spectrum antibiotics also effective

TABLE 2. *Therapeutic Indications for Penicillin in Pediatrics (Continued)*

TYPE OF INFECTION	DRUG OF CHOICE	COMMENT
Fulminating meningococcemia (Waterhouse-Friderichsen syndrome)	Combination penicillin, sulfadiazine & tetracycline Adrenal cortical extract and cortisone	Extremely vigorous therapy indicated. Aqueous crystalline penicillin 1,000,000 units every 3 hrs. IM; sodium sulfadiazine 2–3 grains/lb./24 hrs. IV and tetracyline 30 mg./lb./24 hrs. IV. In addition, adrenal cortical lipoextract 10–20 ml. every 6 hrs. IV and cortisone 100 mg. IV stat and 50–100 mg. IM/day for 3–4 days. Norepinephrine for blood pressure maintenance
Congenital syphilis	Penicillin	Total dose of penicillin is 200,000 units/lb. administered over a treatment period of 7–10 days. Seronegativity usually obtained within 6–12 mos. with improvement in osseous lesions within 1–3 mos. May expect 75% recovery with this regimen. Herxheimer reactions occur in moderate number of cases, but are not usually serious
Diphtheria	Antitoxin Penicillin Erythromycin	Antitoxin is prime feature of treatment. Penicillin or erythromycin useful in eradicating *C. diphtheriae* from nasopharynx
Clostridial infections (tetanus & gas gangrene	Antitoxin and Penicillin	Penicillin to be used both locally and IM, but has no antitoxic use and is to be regarded as adjunctive therapy only. Antitoxin and surgery are still mainstays of treatment

together with a commentary on recommended dosage, duration of therapy and alternative modalities of therapy. It is well to emphasize, however, that recommendations regarding dosage and duration of therapy are perforce only first approximations; in the last analysis, therapy will have to be largely predicated on the severity of the illness and the response of the individual child.

TABLE 3. *Prophylactic Indications for Penicillin in Pediatrics*

DISEASE	COMMENT
Rheumatic fever	Prophylactic therapy indicated in convalescent rheumatic fever cases. Reduction in recurrences approximately 70%. Daily dose of penicillin orally (200,000 units) usually adequate. May also use benzathine penicillin (Bicillin) in dose of 1.2 million units IM once a month. Prophylactic therapy should be administered on year-round basis until child reaches puberty
Oral surgery (i.e., T & A or tooth extraction) in children with congenital or rheumatic heart disease	Penicillin should be given for 2 days before and 3 days after oral surgery in a dose of 300,000 units procaine aqueous penicillin IM daily or 200,000 units orally 4 times a day
Meningococcus contacts	Children exposed to meningococcal meningitis should be treated with oral penicillin (200,000 units 4 times a day) for 4 days. Sulfadiazine good alternative therapy
Diphtheria contacts	If contact is Schick-negative, 300,000 units of aqueous procaine penicillin daily IM or oral penicillin (200,000 units 4 times a day) should be given for 5 days. Erythromycin (20 mg./lb./24 hrs.) excellent alternative therapy
Scarlet fever contacts	Scarlet fever contacts should receive a daily injection of 300,000 units of procaine aqueous penicillin IM or oral penicillin (200,000 units 4 times a day) for 5 days
Bacterial infections complicating viral infections such as measles, influenza, upper respiratory infections, etc.	Frequent bacterial complications in these diseases provide some justification for use of antibiotic agents such as penicillin, especially in infants or young children. Indiscriminate use of drugs should be avoided, however

REFERENCES

1. Ahern, J. J., Burnell, J. M., and Kirby, W. M. M.: Lack of Interference of Chloramphenicol with Penicillin in a Hemolytic Streptococcal Infection in Mice. *Proc. Soc. Exper. Biol. & Med.*, 79:568, 1952.
2. Ahern, J. J., and Kirby, W. M. M.: Lack of Interference of Aureomycin with Penicillin in Treatment of Pneumococcic Pneumonia. *A.M.A. Arch. Int. Med.*, 91:197, 1953.
3. Barrett, H. L., McNamara, H., Shultz, S., and Tompsett, R.: Renal Clearances of Sodium Penicillin G, Procaine Penicillin G and Inulin in Infants and Children. *Pediatrics*, 3:418, 1949.
4. Berkowitz, M., Glaser, J., and Johnstone, D. E.: Incidence of Allergy to Drugs in Pediatric Practice. *Ann. Allergy*, 11:561, 1953.
5. Bunn, P. A., McDermott, W., Hadley, S. J., and Carter, A. C.: Treatment of Pneumococcic Pneumonia with Orally Administered Penicillin. *J.A.M.A.*, 129:320, 1945.
6. Coriell, L. I., McAllister, R. M., Preston, E., and Hunt, A. D.: Scarlet Fever and Mixed Infections of the Throat and Nasopharynx Treated Orally with

Dibenzyl Ethylene Diamine Dipenicillin G. *Antibiotics & Chemother.*, 3:357, 1953.

7. Dowling, H. F., Sweet, L. K., Robinson, J. A., Zeller, W. W., and Hirsh, H. L.: The Treatment of Pneumococcic Meningitis with Massive Doses of Systemic Penicillin. *Am. J. M. Sc.*, 217:149, 1949.
8. Dowling, H. F., Lepper, M. H., and Jackson, G. G.: Observations on the Epidemiological Spread of Antibiotic-Resistant Staphylococci, with Measurement of the Changes in Sensitivity to Penicillin and Aureomycin. *Am. J. Pub. Health*, 43:860, 1953.
9. Eagle, H., Fleischman, R., and Levy, J.: Continuous vs. Discontinuous Therapy with Penicillin. *New England J. Med.*, 248:481, 1953.
10. Eagle, H., Fleischman, R., and Musselman, A. D.: Effect of Schedule of Administration on the Therapeutic Efficacy of Penicillin. Importance of the Aggregate Time Penicillin Remains at Effectively Bactericidal Levels. *Am. J. Med.*, 9:280, 1950.
11. Hildick-Smith, G., Scott, T. F. M., and Whitlock, M.: Penicillin Regimens in Pediatric Practice: Study of Blood Levels. *Pediatrics*, 5:97, 1950.
12. Jawetz, E., Gunnison, J. B., and Speck, R. S.: Studies on Antibiotic Synergism and Antagonism: The Interference of Aureomycin, Chloramphenicol and Terramycin with the Action of Streptomycin. *Am. J. M. Sc.*, 222:404, 1951.
13. Jawetz, E., and Speck, R. S.: The Joint Action of Penicillin with Chloramphenicol on an Experimental Streptococcal Infection of Mice. *Proc. Soc. Exper. Biol. & Med.*, 74:93, 1950.
14. Kohn, K. H., Melzer, A., and MacLean, H.: Prophylaxis of Recurrences of Rheumatic Fever with Penicillin Given Orally. *J.A.M.A.*, 151:347, 1953.
15. Lepper, M. H., and Dowling, H. F.: The Treatment of Pneumococcic Meningitis with Penicillin Alone Compared with Penicillin Plus Aureomycin, Including Observations on an Apparent Antagonism between Penicillin and Aureomycin. *A.M.A. Arch. Int. Med.*, 88:489, 1951.
16. Levin, S. J., and Moss, S. S.: Repository Penicillin Injections in Allergic Children. *Ann. Allergy*, 9:471, 1951.
17. Ludlam, G. B.: *J. Hyg.*, 51:64, 1953.
18. Needham, G. M., and Nichols, D. R.: Recent Changes in Sensitivity of Micrococcus Pyogenes to Various Antibiotic Agents. *J. Lab. & Clin. Med.*, 41:150, 1953.
19. Ross, S., Burke, F. G., and McLendon, P. A.: Penicillin by Mouth: Report of a Clinical Trial. *J.A.M.A.*, 129:327, 1945.
20. Ross, S., Burke, F. G., and Olansky, S.: Oral Administration of Penicillin. *New England J. Med.*, 236:817, 1947.
21. Ross, S.: Unpublished data.
22. Stollerman, G. H., and Rusoff, J. H.: A New Long Acting Repository Penicillin. Prophylaxis against Group A Streptococci in Patients with Rheumatic Fever. *J.A.M.A.*, 150:1571, 1952.
23. Walker, S. H.: A Study of the Possible Interference of Chloramphenicol with Penicillin in Acute Streptococcal Pharyngitis. *Antibiotics & Chemother.*, 3:677, 1953.

2125 — 13th Street, N.W.
Washington, D.C.

STREPTOMYCIN AND DIHYDROSTREPTOMYCIN

Applied Pharmacology

HARRY KING, M.D.

SAMUEL KARELITZ, M.D.

In 1944 the isolation of streptomycin from two cultures of streptomycin-producing strains of *Streptomyces griseus* was reported by Waksman and his group.[62] This actinomycete is a member of a group of fungi and occurs in manure, compost, river mud, animal excreta, water, dust and soils.[20]

SOURCE

After the original report, purification of the antibiotic was undertaken by many workers.[7, 18, 36, 38] Attempts were made to improve its production by altering the media on which the *Streptomyces griseus* grew, using a soybean meal medium,[55] a yeast extract,[39] synthetic media[66] and organic nitrogen sources.[12, 14] In an effort to produce high streptomycin-yielding strains, the actinomycete was irradiated. However, the superior strains produced were extremely unstable and reverted to the parent type.[61]

Commercially, the antibiotic is produced by the submerged-culture technique in fermentation tanks.[20] The exact biochemical pathways by which *S. griseus* produces streptomycin are still unknown. It has been shown that when the microorganism is grown in the presence of $C^{14}O_2$, the carbon of the guanidine side chains in streptomycin was derived from the carbon dioxide which was supplied.[28] Dihydrostrepto-

From the Long Island Jewish Hospital, New Hyde Park, New York.

mycin is obtained by the catalytic hydrogenation of streptomycin and is similar to it in antibacterial spectrum and potency. However, it is more stable than streptomycin and, while being less injurious to the vestibular apparatus, is more toxic to the auditory senses.[20]

CHEMISTRY

Streptomycin is a levorotatory, triacidic base, with the molecular composition $C_{21}\ H_{39}\ N_7\ O_{12}$. It forms various salts of which the sulfate, $2(C_{21}\ H_{39}\ N_7\ O_{12})\ 3H_2\ SO_4$, the trihydrochloride, and calcium chloride double salt, $2(C_{21}\ H_{39}\ N_7\ O_{12} \cdot 3HCl)$, $Ca\ Cl_2$, are of commercial importance.[56] The latter salt is of great aid in eliminating impurities in crude streptomycin concentrates.[50] All the salts are

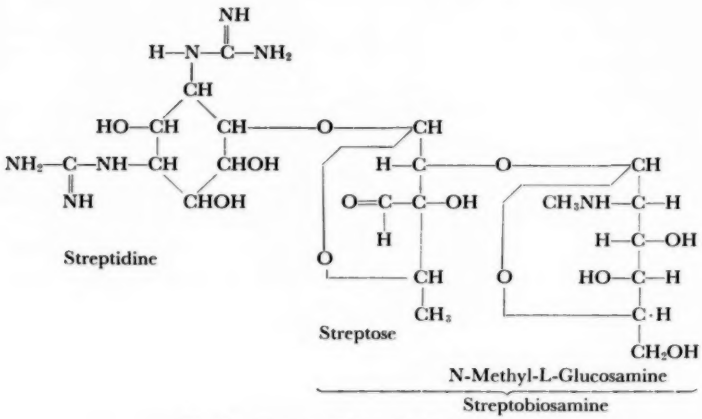


Fig. 6. Structural formula of streptomycin.

readily soluble in water. The base is insoluble in chloroform and ether, but is soluble in alcohol. The hydrochloride salt is soluble in methyl alcohol and thus differs from the sulfate, which precipitates from methyl alcohol solutions.[56]

Chemically, streptomycin is composed of three moieties: streptidine, streptose, and N-methyl-L-glucosamine joined together by glycosidic linkages.[37]

In acids the weaker glycosidic bond in streptomycin, between streptidine and streptose, is hydrolyzed to give streptobiosamine and streptidine.[51] It is the streptidine which probably accounts for the delayed neurotoxic effect of the streptomycin molecule.[20] Streptobiosamine is a disaccharide consisting of N-methyl-L-glucosamine and streptose,

which is a pentose containing the reactive aldehyde group associated with the streptomycin molecule.[35] The reduction of the aldehyde to an alcohol group by hydrogenation with platinum or nickel gives dihydrostreptomycin. Unlike streptomycin, dihydrostreptomycin is stable to alkali and can be crystallized as a base. However, it does not form a calcium chloride double salt.[52]

Streptomycin is stable both in dry form and in solution. Solutions at pH 3 to 7 can be kept for at least 60 days at temperatures of 7 to 25° C. In the dry form it can be kept for at least two years at room temperature. The drug is less active in an acid than a slightly alkaline medium and, unlike penicillin, is not inhibited by any known bacterial enzyme.[20]

MODE OF ACTION

Although there is no certainty about the exact mechanism by which streptomycin exerts its antibacterial effects, the prevalent theory is that it inhibits the oxalacetate-pyruvate condensation, which is part of the oxidation-reduction reaction in the bacterial cell.[69] The host cell is not affected by the drug because it is safeguarded by the cell wall and a barrier at the surface by the mitochondria, both of which are impermeable to streptomycin. Since the oxalacetate-pyruvate condensation occurs in the mitochondria, the host cell is doubly protected.[68]

ABSORPTION

The parenteral route of administration of streptomycin is the one which affords the most satisfactory absorption. After an intravenous inoculation the blood level of the drug rises immediately to a peak. After intramuscular injection absorption is slower and peak levels occur 30 minutes to three hours later, with a mean time of about 90 minutes. Subcutaneous injection gives peak levels 45 minutes to three hours later, with a mean time of about two hours.[54]

Absorption is poor from the alimentary canal. The reason for this is not understood, but is not due to inactivation, since large amounts can be recovered in the feces after oral ingestion.[65] However, occasionally in man one sees high and sustained blood levels after rectal administration.[46]

There appears to be only little absorption through the lungs,[24] and that from the pleural and peritoneal cavities is only slightly better.[20] If the meninges are normal and free from inflammation, the absorption from the cerebrospinal fluid into the blood is as poor as passage in the reverse direction.[46] And finally, little or no streptomycin penetrates the intact skin, cornea or mucosa.[54]

DISTRIBUTION

Streptomycin is distributed primarily in the extracellular fluid compartment. Since it penetrates erythrocytes poorly, the concentration in plasma is nearly twice that in whole blood.[20] Postmortem studies in man showed that when death occurred while the patient was under treatment with streptomycin, clinically significant amounts were found in the kidney, liver, muscle and thyroid, but none in the lymph nodes, spleen, testes, lung or brain. Only traces were found in the prostate and pancreas.[53]

The drug passes readily from the blood into the peritoneal fluid, particularly where some pathologic process is present; the levels in peritonitis may equal serum levels.[6] However, diffusion into the pleural fluid is not as good, levels reaching only one-quarter to one-half that of the serum.[53] In empyema fluid the levels of streptomycin are low, only 1 unit per milliliter three and one-half hours after a single intramuscular injection of between 500,000 and 1,000,000 units of streptomycin.

Whereas streptomycin enters the cerebrospinal fluid slowly and to a limited extent normally, in the presence of meningitis the levels in this fluid are about one-third to one-half of the plasma concentration of the drug. Approximately similar concentrations can be found in joint fluid after intramuscular injection, in patients with infectious arthritis and in pericardial fluid.[20] However, adequate concentrations of streptomycin cannot be obtained in the ocular fluids other than the secondary aqueous humor after parenteral injection. Concentrations in the amniotic fluid and fetal plasma reach about 50 per cent of that in maternal plasma.[74]

EXCRETION

The preponderance of excretion of streptomycin is through the kidneys. With normal kidney function 30 to 60 per cent of the streptomycin administered parenterally may be expected to appear in the urine within 24 hours. The most rapid excretion occurs in the first two to four hours, and most of the antibiotic appears in the urine during the first 12 hours.[54]

The rate of renal clearance of streptomycin is lower than the glomerular filtration rate as determined by the thiosulfate clearance method, about 38 to 67 ml. of plasma being cleared of the drug per minute.[1] Since clearance of the drug does not depend on variations in its plasma concentration or in the rate of urine flow, tubular reabsorption is unlikely. The lowered clearance rate is adequately explained by the binding of streptomycin by plasma proteins. Because the renal tubules do

not excrete the drug, agents which block tubular excretion have no effect on the plasma concentration of streptomycin.[20]

When renal damage is involved, 2 per cent or less of a parenterally administered dose may be excreted in the urine, the plasma level remaining relatively constant over a period of days. If medication is continued under these circumstances, the plasma level of streptomycin can easily rise to toxic levels.[54]

A small portion of parenterally administered streptomycin is secreted by the liver into the bile. After a single intravenous dose of 600,000 units, traces of the drug were present in the bile within one hour and peak levels as high as 7.5 micrograms per milliliter were recorded.[77] A small amount may also be excreted in the feces. After administration of 4,000,000 units of streptomycin daily by the intravenous route, 100 to 130 units of the antibiotic per gram of feces was found.[45] How much of this originated from the bile is not known.

It is apparent, then, that 10 to 30 per cent of the parenterally administered drug is not accounted for by excretion. Since, when there is renal insufficiency, constant plasma levels of streptomycin occur for long periods, it is also apparent that the drug is not readily changed to inactive substances in the tissues, and no degradation product of streptomycin has been identified. It is postulated that storage of the drug in the body may account for its incomplete excretion.[20]

ABSORPTION, DISTRIBUTION AND EXCRETION OF DIHYDROSTREPTOMYCIN

The absorption, distribution, fate and excretion of dihydrostreptomycin are similar in all respects to those of streptomycin, both in animals and in man.[20]

ADMINISTRATION AND DOSAGE

Intermittent deep intramuscular injection of streptomycin is the method of choice for administration. The most satisfactory solution of the drug for intramuscular dosage is one which contains 200 mg. of streptomycin per milliliter of distilled water. Although some of the more highly purified preparations of the drug are well tolerated when administered subcutaneously, this route is not as satisfactory as the intramuscular one.[25]

In the adult 0.5 gm. of streptomycin every six hours intramuscularly has been shown to yield adequate blood levels for the treatment of most infections.[40] The recommended daily dose for children is 40 to 50 mg. per kilogram.[31] Except in tuberculosis and subacute bacterial endocarditis, it is seldom necessary to administer the drug for longer than seven to 14 days.[25] Dosage should be adequate initially to cure

the infection as quickly as possible before the involved bacteria become resistant to streptomycin.[3]

Intravenously, the total daily dose may be administered in a liter of physiologic saline solution at the rate of 20 to 25 drops per minute. This route, however, has no advantage over the intramuscular and in addition is often associated with venous irritation.[25] Because of the increased likelihood of ototoxic manifestations, dihydrostreptomycin should never be given intravenously.[20]

Streptomycin may also be given intrathecally. Again dihydrostreptomycin should not be used because of the increased danger of ototoxicity. The dose should not be over 1 mg. per pound of body weight and should not exceed 50 to 100 mg. totally. It should be given slowly diluted in 5 to 10 cc. of physiologic saline solution.[20, 25]

The intrathoracic or intraperitoneal routes may be used in cases of empyema or peritonitis to supplement systemic therapy. The instillation of solutions of 0.5 to 1.0 gm. of streptomycin in 20 to 50 cc. of physiologic saline solution can be performed into either the thoracic or peritoneal cavities. In the presence of empyema the pus should be evacuated prior to the instillation of the drug.[47]

Oral administration of streptomycin is utilized for local antibacterial effects in the intestinal tract, since the drug is not absorbed through the intestinal wall, nor is it destroyed by passage through the gut. Preoperatively in bowel surgery, streptomycin is used prophylactically to eliminate sensitive microorganisms from the stool. It is started two or three days prior to operation, the dose being 0.5 to 1.0 gm. every six hours orally, and is continued five to seven days postoperatively.[33] The drug is also used orally to treat diarrheas when streptomycin-sensitive organisms are the causative agents.[19] In these cases the oral route may have to be combined with the parenteral one.

Streptomycin also may be administered by inhalation of an aerosol. This is useful as a supplement to systemic therapy in respiratory infections caused by streptomycin-sensitive organisms. A solution containing 50 mg. of streptomycin in 1 cc. of sterile saline solution is used for inhalation every three hours.[47]

Finally, the drug has been used topically. However, this is not recommended because of the danger of local cutaneous reactions and sensitization.[20]

BLOOD AND URINARY LEVELS

The plasma concentration of streptomycin varies with the dose, method of administration, and renal function. Intravenous administration yields higher but less sustained levels; 0.25 to 0.5 gm. given rapidly intravenously yields plasma levels of 25 to 50 micrograms per

milliliter. This falls to 3 to 5 micrograms within six hours after injection. Intramuscularly comparable doses yield about one-half of the peak values obtained by comparable intravenous doses, but the peak is reached in one or two hours and falls slowly.

In the adult 0.5 gm. of the drug given every six hours intramuscularly yields plasma levels between 7 and 15 micrograms per milliliter, which are usually effective against most streptomycin-sensitive microorganisms. This dosage will also yield urinary levels of 200 to 1500 micrograms per milliliter, depending on clearance rate, renal function and urine volume.[20]

COMPLICATIONS

The toxic reactions to streptomycin and dihydrostreptomycin may be described under the following categories:

Hypersensitivity Reactions

These reactions usually manifest themselves as skin eruptions, fever, eosinophilia and blood dyscrasias; however, severe anaphylactoid reactions have also been reported after the injection of streptomycin.[71]

The toxic eruption seen with streptomycin therapy usually occurs during the second week and is indistinguishable from that caused by other drugs. The incidence of this complication has been set at 5 to 18 per cent in the over-all population. Even more common are cases of contact dermatitis among professional personnel handling the drug.[4, 5] The following morphologic types are seen: maculopapular eruptions, erythemas, exfoliative dermatitis, urticaria, morbilliform and scarlatiniform eruptions, purpura, erythema multiforme-like eruptions and erythema nodosum. These skin manifestations may be isolated, or associated with fever, eosinophilia, lymphadenopathy and arthritis. If symptoms are severe, the drug should be withdrawn; however, mild rashes have been known to disappear even with continuation of therapy.[9, 16, 43]

Drug fever has been observed in as many as 7 per cent of patients after medication with streptomycin. This may or may not be associated with other constitutional symptoms resembling serum sickness and may subside in spite of continuation of therapy.[6, 20]

Eosinophilia may reach levels as high as 25 to 40 per cent frequently and in itself does not make necessary interruption of streptomycin therapy.[41] Other more serious hematologic abnormalities, e.g., agranulocytosis,[8] aplastic anemia,[75] hemorrhagic purpura[34] and thrombocytopenia,[60] are much less common, their over-all incidence following streptomycin therapy being less than 1 per cent.

Vestibular-Auditory Disturbances

Damage to the eighth cranial nerve is the most important danger in the use of streptomycin. It was noted soon after the clinical use of the drug began in 1945.[27]

In patients given 2 gm. of streptomycin per day for four weeks, up to 96 per cent have suffered from vertigo. Before vertigo develops there is usually headache, nausea and vomiting. This is followed by signs of ataxia.[41] If the drug is discontinued when signs of vestibular dysfunction first appear, these signs are reversible. However, continued administration results in permanent changes.[47] Usually the patient is able to learn to compensate for his labyrinthine damage, but symptoms of vertigo can then be elicited when the eyes are closed.[20]

Auditory disturbances, while less common than the vestibular, can affect up to 15 per cent of patients treated with streptomycin.[8] Tinnitus is usually the first symptom of impending difficulty, and if the drug is stopped at this point, permanent auditory impairment can usually be avoided.[20]

In contrast to streptomycin, dihydrostreptomycin is more likely to affect auditory rather than vestibular function. The impairment of hearing with dihydrostreptomycin may become apparent after the drug has been stopped and can progress rapidly and become permanent. Because loss of auditory function is much more distressing than vestibular involvement, particularly since vertigo usually can be compensated for, the use of dihydrostreptomycin is discouraged when long-term medication is necessary.[22]

The exact anatomic site where either of these drugs exerts its auditory or vestibular damage has not been determined; evidence has been produced to show end organ involvement, but some workers believe that the effect is on the central nuclei.[23, 72]

Usually the intensity of injury to the eighth nerve depends on the daily dose and the duration of therapy,[73] but this is not always so.[70] Also the danger of neurotoxicity is usually greater with intrathecal medication and when there is meningeal inflammation. Especially in renal impairment, even small doses can cause damage because of the high plasma levels of the drug.[30]

It is important, because of the seriousness of eighth nerve injury, that patients on long-term regimens of streptomycin be watched closely for signs of damage and be subjected to repeated audiometric and labyrinthian tests.[47]

Intrathecal Irritation

A reaction characterized by a shocklike state with convulsions and signs of cerebellar injury has been described in as high as 15 per cent

of patients receiving intrathecal streptomycin.[42] This is more apt to occur when excessive doses are used, e.g., more than 100 mg. in an adult, and 25 mg. in a child intrathecally.

Miscellaneous Reactions

Nausea and vomiting have only occasionally been seen with streptomycin therapy.[8] Similarly unusual are stomatitis[49] and black furry tongue.[67] Renal injury has been reported, but is rare and usually mild when it occurs.[70]

In addition to the toxic manifestations mentioned it should be pointed out that prolonged therapy with streptomycin may suppress gram-negative bacilli, but stimulate superinfection with gram-positive cocci (particularly *Staphylococcus pyogenes*), yeast and fungi.[63]

ACTIVITY IN VITRO

Streptomycin's antimicrobial action in vitro has been described as bacteriostatic in low concentrations and bactericidal in high concentrations.[48] There are factors other than concentration, however, which may influence the degree of bacteriostatic or bactericidal action in vitro. The pH of the medium is important, since the drug is more active in a slightly alkaline medium. Activity also depends on the relative sensitivity of the organism and on the number of organisms, since with a larger bacterial population the concentration of streptomycin required to inhibit growth is greater.[76]

The drug has a wide spectrum of antibacterial action in vitro, particularly against the gram-negative bacilli. The following microorganisms are regarded as being highly sensitive to streptomycin, since their growth usually is inhibited by less than 10.0 micrograms per milliliter of the antibiotic:

Actinomyces
Bacillus anthracis
Brucella abortus
Brucella melitensis
Brucella suis
Donovania granulomatis
Erysipelothrix rhusiopathiae
Hemophilus influenzae
Hemophilus pertussis
Klebsiella pneumoniae
Leptospira icterohaemorrhagiae
Listeria monocytogenes
Mycobacterium tuberculosis var. hominis
Mycobacterium tuberculosis var. bovis
Neisseria meningitidis (intracellularis)
Pasteurella multocida
Pasteurella pestis
Salmonella species
Salmonella typhosa (Eberthella typhosa)
Shigella dysenteriae
Shigella paradysenteriae
Streptobacillus moniliformis
Veillonella gazogenes

Those organisms the growth of the majority of which is inhibited by between 10.0 and 100.00 micrograms of streptomycin per milliliter, are classified as moderately sensitive. In this group are included the following:

Aerobacter aerogenes
Alcaligenes faecalis
Corynebacterium diphtheriae
Diplococcus pneumoniae
Escherichia coli
Hemophilus ducreyi
Malleomyces mallei
Nocardia asteroides
Proteus morgani
Proteus aeruginosa
Pseudomonas aeruginosa
Rickettsia akari
Rickettsia burneti
Ricksettsia prowasekii
Rickettsia typhi
Staphlylococcus albus
Staphylococcus aureus
Streptococcus alpha hemolytic
Streptococcus beta hemolytic
Streptococcus faecalis
Vibrio chlolerae

Finally, the insensitive organisms, or those that require more than 100 micrograms of streptomycin per milliliter to inhibit their growth, are as follows:

Bacteroides fragilis
Bacteroides fundiliformis
Clostridium species
Malleomyces pseudomallei
Rickettsia tsutsugamushi
Viruses
Blastomyces dermatiditis
Candida albicans
Coccidioides immitis
Cryptococcus neoformans
Geotrichum species
Histoplasma capsulatum
Entamoeba histolytica
Trichomonas vaginalis
Trypanosoma species

It cannot be assumed that species highly susceptible in vitro will be equally susceptible in vivo. This is well illustrated by the relative ineffectiveness of streptomycin therapy for the treatment of Brucella, Salmonella and Shigella infections in human beings. Highly susceptible organisms usually respond more readily in vivo to streptomycin than those moderately sensitive, and those very resistant in vitro respond not at all in vivo.[76]

Streptomycin Resistance and Dependence

Resistance. A great disadvantage of streptomycin is the frequent development of bacterial resistance to the drug, particularly when it is used for a long period. Marked resistance appears more rapidly when the original bacterial population is large, because there is then a greater likelihood that there are present a few highly resistant bacteria, which then give rise to subsequent generations of streptomycin-refractory bacteria.[2] There is also a possibility that cells initially sensitive to the drug can become adapted to it as a result of exposure. That an organism is resistant does not mean that it has lost any of its virulence.[20]

Dependence. Certain strains of bacteria are not only resistant to streptomycin, but also are dependent on it for growth. This dependence is usually thought to be inherited, rising out of mutations. These organisms do not cause infection unless streptomycin is given.[45]

INDICATIONS

Because of its toxicity and the frequency of rapid development of bacterial resistance, the use of streptomycin should be limited to infections produced by organisms which are sensitive to the drug and for which an effective and less toxic antibacterial preparation is not available.[47] It is often an important therapeutic agent in urinary tract infections, subacute bacterial endocarditis, meningitis, bacteremias and pneumonias if other antibiotics are not effective against the causative organism, and is still extremely important in the therapy of tuberculosis. Other diseases in which the drug is of value are tularemia, granuloma inguinale, plague and brucellosis.

In urinary tract infections the drug is mainly effective against the gram-negative bacilli, primarily *E. coli, P. vulgaris, A. aerogenes, Ps. aeruginosa, H. influenzae, K. pneumoniae* and also *Streptococcus faecalis* and *M. tuberculosis.* Since many strains of these organisms have become resistant to streptomycin, sensitivity tests should be carried out prior to the institution of therapy.[26]

There is usually good agreement between clinical results and observations in vitro if the pH of the urine is maintained as near 8.0 as possible; hence the administration of alkali with streptomycin is important. When the drug is effective, it usually kills bacteria so rapidly that therapy ought not usually to be prolonged past four or five days. Bacteriologic control of acute infections of the urinary tract is about 60 to 80 per cent effective with streptomycin, and failures are usually due to the emergence of resistance, the neglect to use alkali with the drug, or persistence of urinary obstruction.[33]

Although streptomycin may prove lifesaving in the treatment of meningitis caused by any sensitive organism, its primary use, other than in tuberculous meningitis, is in influenzal meningitis. Prior to the advent of Chloromycetin, streptomycin was the drug of choice in meningitis caused by *H. influenzae,*[10] and even now its use, combined with Chloromycetin, is recommended by many, particularly in the more severe cases.[31]

In infections (e.g., pneumonia, meningitis, bacteremias) caused by *K. pneumoniae* streptomycin is particularly useful and has lowered the over-all mortality from 94 to 20 per cent.[58]

Streptomycin has markedly lowered the morbidity, mortality and re-

lapse rate in all forms of tularemia. However, since the tetracyclines are usually equally effective, they are the drug of choice. Granuloma inguinale also responded well to streptomycin,[21] but here too the tetracyclines are preferred.

Streptomycin is highly specific in the treatment of plague, reducing the mortality from the former 40 to 90 per cent to 4 to 10 per cent. It should be administered with sulfadiazine, and usually the patient responds favorably in two or three days.[44] In brucellosis a combination of streptomycin and sulfadiazine will result in a clinical and bacteriologic recovery in about 67 per cent of cases and is helpful in controlling severe complications, such as bacterial endocarditis, osseous lesions and neurologic lesions.[64]

In the treatment of tuberculosis, prior to the advent of isoniazid, streptomycin was the principal chemotherapeutic agent. In addition to its toxicity, the principal disadvantage of streptomycin is the fact that 70 per cent of positive cultures are resistant to significant levels of the drug after three months of treatment. There is a delay in development of resistance when combined therapy is used, and when combined with para-aminosalicylic acid the resistance after three months has been reduced to 10 per cent.

At present the Committee on Therapy of the American Trudeau Society feels that isoniazid should always be included with streptomycin in the treatment of the more dangerous forms of tuberculosis, such as miliary, meningeal and acute extensive pneumonic pulmonary tuberculosis. The streptomycin may be given daily, 1 gm. intramuscularly, or twice weekly, but is apparently more effective when it is given uninterruptedly. Treatment should continue at least one year, but more often 18 months or longer.[13]

Unfortunately, streptomycin has failed to modify significantly typhoid or salmonella diseases even though from sensitivity in vitro, results would have been expected to be good. The drug, however, temporarily suppresses bacterial flora in feces when given orally and is, therefore, used to sterilize the bowel prior to operation.[57] It has also been used orally in the treatment of shigellosis;[59] however, other antibiotics are to be preferred.

In diphtheria, although usually other agents are preferable, streptomycin has been shown in one case at least to eradicate the organism when penicillin and Aureomycin failed.[32] Because of the marked sensitivity in vitro of *H. pertussis* to streptomycin, the drug has been used in the treatment of pertussis. The results have been equivocal, some observers reporting clinical improvement. However, the broad-spectrum antibiotics are at least equally effective and their use is to be preferred.[31]

Potentiation of Streptomycin by Combination Therapy

According to the grouping of Jawetz and Gunnison, streptomycin may be synergistic with penicillin, bacitracin and neomycin, but may be antagonistic to the broad-spectrum antibiotics if a relatively ineffective dose of one drug is added to a therapeutically effective concentration of another. This antagonism is believed to be the result of the retardation of bacterial growth by the broad-spectrum antibiotics, making streptomycin less effective.[29] These phenomena of antagonism and synergism seem well established in the laboratory, but clinical evidence is not easily demonstrated.[31]

Combinations of streptomycin with another agent are necessary in mixed infections in which one antibiotic may be effective against one bacterial species and the second against another, e.g., penicillin and streptomycin in peritonitis. They also may prevent the development of superinfections which would develop if streptomycin were used alone, e.g., penicillin used with streptomycin to prevent superinfection with gram-positive organisms. Finally, as in the case of PAS used with streptomycin in the therapy of tuberculosis, combination therapy may delay the development of bacterial resistance.[11]

REFERENCES

1. Adcock, J. D., and Hettig, R. A.: Absorption, Distribution and Excretion of Streptomycin. *Arch. Int. Med.*, 77:179, 1946.
2. Alexander, H. E., and Leidy, G.: Induction of Streptomycin Resistance in Sensitive Hemophilus Influenzae by Extracts Containing Desoxyribonucleic Acid from Resistant Hemophilus Influenzae. *J. Exper. Med.*, 97:17, 1953.
3. Alexander, H. E., and Leidy, G.: Mechanism of Emergence of Resistance to Streptomycin in Five Species of Gram-Negative Bacilli. *Pediatrics*, 4:214, 1949.
4. Amsler, R.: Allergic Accidents Induced by Streptomycin. *Presse méd.*, 59: 1011, 1951.
5. British Ministry of Health, Editorial: Sensitization of Nursing Staff to Antibiotics. *Brit. M.J.*, 2:39, 1954.
6. Buggs, C. W., Pilling, M. A., Bronstein, B., and Hirshfeld, J. W.: Absorption, Distribution and Excretion of Streptomycin in Man. *J. Clin. Investigation*, 25:94, 1946.
7. Carter, H. E., and others: Isolation and Purification of Streptomycin. *J. Biol. Chem.*, 160:337, 1945.
8. Council Report: The Effect of Streptomycin on Tuberculosis in Man. *J.A.M.A.*, 135:634, 1947.
9. Crissey, J. T., and Caccamise, W.: Antibiotic Drug Eruptions. *New York State J. Med.*, 53:2085, 1953.
10. Crook, W. G., Clanton, R. R., and Hodes, H. L.: Hemophilus Influenzae Meningitis: Observations on the Treatment of 110 Cases. *Pediatrics*, 4:643, 1949.
11. Dowling, H. F.: The Present Status of Antibiotic Therapy. *Antibiotics & Chemother.*, 1:2, 1951.
12. Dulaney, E. L.: Observations on Streptomyces Griseus. II. Nitrogen Sources for Growth and Streptomycin Production. *J. Bact.*, 56:305, 1948.

13. Ebert, R. H.: Present Status of the Chemotherapy of Tuberculosis. *Am. J. Med.*, 18:738, 1955.
14. Eiser, H. M., and McFarlane, W. D.: Studies on the Metabolism of Streptomyces Griseus in Relation to the Production of Streptomycin. *Canad. J. Research*, 26C:164, 1948.
15. Elias, W. F., and Durso, J.: Blood, Urine and Fecal Levels of Streptomycin in the Treatment of Human Infections of E. Typhosa. *Science*, 101:589, 1945.
16. Fein, B. T., and Criep, L. H.: Exfoliative Dermatitis from Dihydrostreptomycin. *Texas State J. Med.*, 46:712, 1950.
17. Foshay, L.: Tularemia, in Waksman, S. A., ed.: *Streptomycin, Nature and Practical Applications*. Baltimore, Williams & Wilkins Company, 1949, Chap. 23.
18. Fried, J., and Wintersteiner, O.: Crystalline Reineckates of Streptothricin and Streptomycin. *Science*, 101:613, 1945.
19. Goettsch, E., Colbey, G., and Mulloy, M.: Treatment of Infantile Diarrhea with Streptomycin and Oral Amigen Mixture. *Pediatrics*, 2:1, 1948.
20. Goodman, L. S., and Gilman, A.: *The Pharmacological Basis of Therapeutics*. 2nd ed. New York, Macmillan Company, 1955.
21. Greenblatt, R. B.: Therapy of Granuloma Inguinale, in Waksman, S. A., ed.: *Streptomycin, Nature and Practical Applications*. Baltimore, Williams & Wilkins Company, 1949, Chap. 35.
22. Harrison, W. H.: Ototoxicity of Dihydrostreptomycin. *Quart. Bull. Northwestern Univ. M. School*, 28:271, 1954.
23. Hawkins, J. E., Jr., and Lurie, M. H.: The Ototoxicity of Streptomycin. *Ann. Otol., Rhin. & Laryng.*, 61:789, 1952.
24. Heilman, D. H., Heilman, F. R., Hinshaw, H. C., Nichols, D. R., and Herrell, W. E.: Streptomycin: Absorption, Diffusion, Excretion and Toxicity. *Am. J. M. Sc.*, 210:576, 1945.
25. Herrell, W. E.: Methods of Administration and Dosage, in Waksman, S. A., ed.: *Streptomycin, Nature and Practical Applications*. Baltimore, Williams & Wilkins Company, 1949, Chap. 14.
26. Hewitt, W. L.: Urinary Tract Infections, in Waksman, S. A., ed.: *Streptomycin, Nature and Practical Applications*. Baltimore, Williams & Wilkins Company, 1949, Chap. 30.
27. Hinshaw, H. C., and Feldman, D. W. M.: Streptomycin in Treatment of Clinical Tuberculosis. *Proc. Staff Meet., Mayo Clin.*, 20:313, 1945.
28. Hunter, G. D., Herbert, M., and Hockenhull, D. J.: Actinomycete Metabolism; Origin of the Guanidine Groups in Streptomycin. *Biochem. J.*, 58:249, 1954.
29. Jawetz, E., and Gunnison, J. B.: An Experimental Basis of Combined Antibiotic Action. *J.A.M.A.*, 150:693, 1952.
30. Jonghees, L. B. W., and Hulk, J.: The Action of Streptomycin on Vestibular Function. *Acta Oto-Laryng.*, 38:225, 1951.
31. Karelitz, S.: Choice of an Antibiotic. *J. Pediat.*, 42:478, 1953.
32. Karelitz, S., King, H., and Rubenstein, I. S.: Aureomycin Treatment of Diphtheria and Diphtheria Carriers. *J. Pediat.*, 39:544, 1951.
33. Kass, E. H.: Chemotherapeutic and Antibiotic Drugs in the Management of Infections of the Urinary Tract. *Am. J. Med.*, 18:764, 1955.
34. Keefer, C. S.: Streptomycin in the Treatment of Infections. *J.A.M.A.*, 132:4, 1946.
35. Kuehl, F. A., Jr., Flynn, E. H., Bishop, M. N., and Folkers, K.: Streptomyces Antibiotics. XIX. Dihydrostreptosonic Acid Lactone and Configuration of Streptose and Streptobiosamine. *J. Am. Chem. Soc.*, 70:2613, 1948.
36. Kuehl, F. A., Jr., Peck, R. L., Hoffkine, C. E., Jr., Graber, R. P., and Folkers, K.: Streptomyces Antibiotics. VIII. Isolation of Streptomycin. *J. Am. Chem. Soc.*, 68:1460, 1946.
37. Kuehl, F. A., Jr., Peck, R. L., Hoffkine, C. E., Jr., Peel, E. W., and Folkers, K.: Streptomyces Antibiotics. XIV. The Position of the Linkage of Streptobiosamine to Streptodine in Streptomycin. *J. Am. Chem. Soc.*, 69:1234, 1947.

38. Kuehl, F. A., Jr., Peck, R. L., Walti, A., and Folkers, K.: Crystalline Salts of Streptomycin and Streptothricin. *Science*, 102:34, 1945.
39. Le Page, G. A., and Campbell, E.: Preparation of Streptomycin. *J. Biol. Chem.*, 162:163, 1946.
40. Loewe, L., and Alture-Werber, E.: Streptomycin Dosage Schedules for Clinical Use. *Bull. New York Acad. Med.*, 23:589, 1947.
41. McDermott, W.: Toxicity of Streptomycin. *Am. J. Med.*, 2:491, 1947.
42. McKay, R. J., Davies, J. A. V., Berenberg, W., and Lowd, H. M., Jr.: Reactions to Intrathecal Streptomycin. *J.A.M.A.*, 147:819, 1951.
43. McKechnie, J. K.: Danger of Therapy in Pulmonary Tuberculosis. *Brit. J. Tuberc.*, 47:150, 1953.
44. Meyer, K. F., and Quan, S. F.: Plague, in Waksman, S. A., ed.: *Streptomycin, Nature and Practical Applications*. Baltimore, Williams & Wilkins Company, 1949, Chap. 25.
45. Miller, C. P., and Bohnhoff: Development of Streptomycin-Resistant and Streptomycin Dependent Bacteria, in Waksman, S. A., ed.: *Streptomycin, Nature and Practical Applications*. Baltimore, Williams & Wilkins Company, 1949, Chap. 10.
46. Molitor, H.: Pharmacology of Streptomycin. *Bull. New York Acad. Med.*, 23:196, 1947.
47. Nelson, W. E.: *Textbook of Pediatrics*. 6th ed. Philadelphia, W. B. Saunders Company, 1954.
48. Paine, T. F., Murray, R., and Finland, M. D.: Streptomycin. I. Bacteriologic and Pharmacologic Aspects. *New England J. Med.*, 236:701, 1947.
49. Palister, R. A.: Death from Dermatitis and Stomatitis during Streptomycin Therapy. *Brit. M.J.*, 2:1271, 1949.
50. Peck, R. L., and others: Streptomyces Antibiotics. II. Crystalline Streptomycin Trihydrochloride-Calcium Chloride Double Salt. *J. Am. Chem. Soc.*, 67:1866, 1945.
51. Peck, R. L., and others: Streptomyces Antibiotics. IV. Hydrolytic Cleavage of Streptomycin to Streptidine. *J. Am. Chem. Soc.*, 68:29, 1946.
52. Peck, R. L., Hoffkine, C. E., Jr., and Folker, K.: Streptomyces Antibiotics. IX. Dihydrostreptomycin. *J. Am. Chem. Soc.*, 68:1390, 1946.
53. Pulaski, E. J., and Sprinz, H.: Streptomycin in Surgical Infections. *Ann. Surg.*, 125:194, 1947.
54. Rake, G., and Donovick, R.: Absorption, Distribution and Excretion of Streptomycin, in Waksman, S. A., ed.: *Streptomycin, Nature and Practical Applications*. Baltimore, Williams & Wilkins Company, 1949, Chap. 14.
55. Rake, G., and Donovick, R.: Studies on the Nutritional Requirements of Streptomyces Griseus for the Formation of Streptomycin. *J. Bact.*, 52:223, 1946.
56. Regina, P.: Chemistry of Antibiotics of Clinical Importance. *Am. J. Med.*, 18:686, 1955.
57. Reimann, H. A.: Intestinal Infections, in Waksman, S. A., ed.: *Streptomycin, Nature and Practical Applications*. Baltimore, Williams & Wilkins Company, 1949, Chap. 31.
58. Riggins, H. M.: Friedlander's Bacillus (Klebsiella Pneumoniae) Infections: Their Treatment with Streptomycin, in Waksman, S. A., ed.: *Streptomycin, Nature and Practical Applications*. Baltimore, Williams & Wilkins Company, 1949, Chap. 26.
59. Ross, S., Burke, F. G., Bischoff, H., Ricci, E. C., and Washington, J. A.: Treatment of Shigella Enteritis with Oral Streptomycin: A Report of 34 Cases. *J.A.M.A.*, 141:83, 1949.
60. Rudensky, H., and Fisher, S.: Thrombopenic Purpura during Streptomycin Treatment of Tuberculous Empyema. *J.A.M.A.*, 147:311, 1951.
61. Savage, G. M.: Improvement in Streptomycin-Producing Strains of Streptomyces Griseus by Ultraviolet and X-ray Energy. *J. Bact.*, 57:429, 1949.
62. Schatz, A., Bugie, E., and Waksman, S.: Streptomycin, a Substance Exhibiting

Antibiotic Activity against Gram-Positive and Gram-Negative Bacteria. *Proc. Soc. Exper. Biol. & Med.*, 57:244, 1944.

63. Smith, D. T.: The Disturbances of the Normal Bacterial Ecology by the Administration of Antibiotics with the Development of New Clinical Syndromes. *Ann. Int. Med.*, 37:1135, 1952.
64. Spink, W. W.: Brucellosis, in Waksman, S. A., ed.: *Streptomycin, Nature and Practical Applications*. Baltimore, Williams & Wilkins Company, 1949, Chap. 24.
65. Stebbins, R. B., Graessle, O. E., and Robinson, H. J.: Studies on Absorption and Excretion of Streptomycin in Animals. *Proc. Soc. Exper. Biol. & Med.*, 60:68, 1945.
66. Thornberry, H. H., and Anderson, H. W.: Synthetic Medium for Streptomyces Griseus and the Production of Streptomycin. *Arch. Biochem.*, 16:389, 1948.
67. Tomaszewski, W.: Incidence of Black Tongue in Antibiotic Therapy. *Brit. M.J.*, 1:1249, 1953.
68. Umbreit, W. W.: Mode of Action of Antibiotics. *Am. J. Med.*, 18:717, 1955.
69. Umbreit, W. W.: A Site of Action of Streptomycin. *J. Biol. Chem.*, 177:703, 1949.
70. Von Oettingen, W. F.: Complications of Antibiotic Therapy. *Am. J. Med.*, 18:792, 1955.
71. Welch, H., Lewis, C. N., Karlan, I., and Putnam, L. E.: Acute Anaphylactic Reaction Attributable to Penicillin. *Antibiotics*, 3:891, 1953.
72. Winston, J.: Clinical Problems Pertaining to Neurotoxicity of Streptomycin Group of Drugs. *A.M.A. Arch. Otolaryng.*, 58:55, 1953.
73. Winston, J., Lewey, F. H., Parenteau, A., Marden, P. A., and Cramer, F. B.: An Experimental Study of the Toxic Effects of Streptomycin on the Vestibular Apparatus of the Cat; The Central Nervous System. *Ann. Otol., Rhin. & Laryng.*, 57:738, 1948.
74. Woltz, J. H. E., and Wiley, M. M.: Transmission of Streptomycin from Maternal Blood to Fetal Circulation and Amniotic Fluid. *Proc. Soc. Exper. Biol. & Med.*, 60:106, 1945.
75. Womack, C. R., and Reiner, C. B.: Fatal Aplastic Anemia Due to Streptomycin. *Ann. Int. Med.*, 34:759, 1951.
76. Youmans, G. P., and Fisher, M. W.: Action of Streptomycin on Micro-Organisms in Vitro, in Waksman, S. A., ed.: *Streptomycin, Nature and Practical Applications*. Baltimore, Williams & Wilkins Company, 1949, Chap. 7.
77. Zintel, N. A., Flippin, H. F., Nichols, A. C., Wiley, M. M., and Rhoads, J. E.: Studies on Streptomycin in Man. I. Absorption, Distribution, Excretion and Toxicity. *Am. J. M. Sc.*, 210:421, 1945.

270–05 — 76th Avenue
New Hyde Park, New York

THE TETRACYCLINES

Applied Pharmacology

HARRY SHWACHMAN, M.D.

AUGUSTO SCHUSTER, M.D.

The tetracyclines comprise three widely used antibiotic agents. Until the elucidation of the chemical structure of these antibiotics, the nomenclature was derived from the species of the actinomyces from which the antibiotics were isolated. Aureomycin, discovered in 1948, is now known as chlortetracycline; Terramycin, introduced in 1950, is oxytetracycline; and a variety of trade-named products such as Achromycin, Tetracyn, Panmycin, Polycycline, Steclin, Pancydine, are referred to as tetracycline. The similarity of these three antibiotics can be seen by examining the structural formulas[2] (see Fig. 7).

SOURCE

Microbiologic methods are still used in the commercial production of chlortetracycline and oxytetracycline. Tetracycline is derived from chlortetracycline by the removal of the chlorine from position 7 by chemical means, although certain species of Streptomyces are known to elaborate tetracycline.

Many clinical and laboratory observations suggest so close a similarity in behavior of these agents that one wonders whether the more recently introduced tetracycline will completely substitute for or replace its analogues. A better tolerance and a greater diffusability plus a diminution in the side reactions prompt such a suggestion. However, any prediction along this line is premature, particularly since a number of

From the Division of Clinical Laboratories and Medicine, Children's Medical Center, and the Department of Pediatrics, Harvard Medical School, Boston.

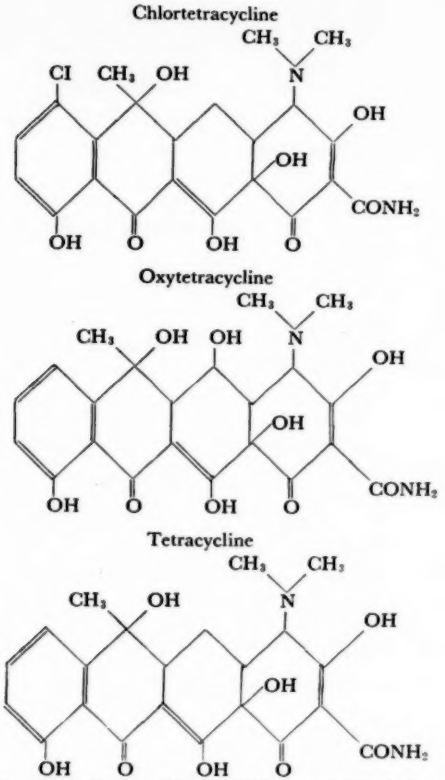


Fig. 7. Structural formulas of chlortetracycline, oxytetracycline and tetracycline.

clinicians prefer to single out one of these agents as superior to the others in the treatment of specific conditions.

SOLUBILITY AND STABILITY

One of the important properties of practical importance is the solubility and stability of the tetracyclines in solution. In general, stability is increased at low temperatures and in an acid medium. In the case of chlortetracycline, considerable activity of neutral solutions is lost in 24 hours at 4° C. Oxytetracycline is more stable with comparable loss in three to four days, whereas tetracycline under similar conditions may retain its activity for three or more weeks. It is therefore necessary to consider this property in assays of biological fluids for antibacterial activity as well as in the determination of the susceptibility of microorganisms to the tetracyclines. Chandler and Bliss[1] clearly pointed out

the rapid rate of deterioration of chlortetracycline in neutral and alkaline solutions and developed a rapid assay method for determining the content of chlortetracycline in body fluids. A practical problem depending on the solubility and stability of solutions is the preparation of commercial products in liquid form acceptable to infants and children. The tetracyclines in dry powder form as the base or hydrochloride are stable indefinitely.

CHEMICAL DIFFERENTIATION

Chemical differentiation of the tetracyclines can be accomplished by a variety of colorimetric reactions, by differences in spectral absorption or by the more complicated Craig countercurrent distribution technique. Of the interesting color reactions which may differentiate these antibiotics, one should mention the reaction of ferric chloride in acidic solutions. All three analogues produce an orange-brown color. However, when chlortetracycline and tetracycline are heated with hydrochloric acid, a stable yellow color develops. This does not happen with oxytetracycline. Oxytetracycline in the presence of sulfuric acid gives a characteristic stable cherry-red solution. In the case of tetracycline a stable violet color develops, and in the case of chlortetracycline a purple-colored solution which changes after a few seconds to a greenish-black. Ehrlich's reagent in dilute hydrochloride acid will produce a bluish-green precipitate with oxytetracycline and a yellowish color with chlortetracycline and tetracycline. Chlortetracycline in alkaline solution develops a blue fluorescence in ultraviolet light, a reaction also given by oxytetracycline, but to a much less extent. The molecular weight of chlortetracycline hydrochloride is 515.34; of oxytetracycline hydrochloride, 496.90; and of tetracycline hydrochloride, 480.90.

ABSORPTION AND EXCRETION; DOSAGE AND ADMINISTRATION

The tetracycline compounds are rapidly absorbed from the gastrointestinal tract when given orally. When given in large single doses, that is, 1 gm., the maximum serum level is reached in two to six hours with a gradual decline to no demonstrable level at the end of approximately 24 hours. In a carefully controlled experiment Wright et al.[7] compared the absorption of the three drugs in 12 healthy subjects. They found levels of tetracycline generally higher than those with the other two analogues. Chlortetracycline levels were slightly lower, and oxytetracycline levels were still lower. Increasing the size of a single dose of the tetracyclines in the range from 1 to 3 gm. does not significantly increase the serum concentrations as one might expect. After multiple doses of 0.25 or 0.5 gm. a gradual increase in the blood concentration

is observed, indicating a cumulative effect. Blood concentrations of the tetracyclines can therefore be maintained by giving repeated doses at six to eight hour intervals. In some instances longer intervals have been advocated, 12 and even 24 hours. It should be pointed out that in some studies a small number of subjects were given what appears to be an adequate dose, yet showed no demonstrable blood level.

Table 4 lists the approximate serum levels in micrograms per milliliter after a single oral dose in healthy adults, comparing chlortetracycline and oxytetracycline. In this table one notes the slightly increased levels with 2 gm. as compared to 1 gm., a somewhat better absorption of chlortetracycline at the 0.5-gm. dose, and finally that serum levels can

TABLE 4. *Approximate Serum Levels in Micrograms per Milliliter after Single Oral Doses in Healthy Adults*

CHLORTETRACYCLINE				OXYTETRACYCLINE			
Time	0.5 Gm.	1.0 Gm.	2.0 Gm.	Time	0.5 Gm.	1.0 Gm.	2.0 Gm.
4 hours	1.4	4.3	6.0	**4 hours**	1.0	2.0	4.6
6 hours	1.4	3.0	4.2	**6 hours**	0.7	3.0	5.0
12 hours	1.0	2.2	3.0	**12 hours**	0.5	2.4	3.9

TABLE 5. *Approximate Serum Concentration in Micrograms per Milliliter after Multiple Oral Doses of 0.5 Gm. Every 6 Hours for 3 Doses in Healthy Adults*

ANTIBIOTIC	6 HOURS	9 HOURS	12 HOURS	15 HOURS	18 HOURS
Oxytetracycline	1.7	3.0	2.2	3.7	3.0
Chlortetracycline	1.6	2.0	2.5	3.0	3.5
Tetracycline	1.0	2.8	2.6	3.1	3.7

be maintained for as long as 12 hours after a single dose. Table 5 lists the levels achieved when 0.5 gm. of the antibiotic is given every six hours for a period of three doses.

Alimentary absorption of the tetracyclines is not modified by foods, but is reduced when the tetracyclines are given with antacids containing aluminum salts. In practice, the administration of the antibiotic with milk is sometimes advocated to minimize some of the local irritating effects. Rectal administration of the tetracyclines should be avoided because of local irritation and irregular and unpredictable absorption.

Intramuscular preparations of chlortetracycline proved to be too irritating and inadequately absorbed and are therefore not available commercially. Oxytetracycline and tetracycline are available for intramuscular injection and have been used satisfactorily in severely ill patients and can be given at eight to 12 hour intervals in the dosage of 4 to 6 mg. per kilogram for 24 hours for oxytetracycline and 10 mg. per kilogram for 24 hours for tetracycline. In an adult with 100 mg.

given every six hours, adequate plasma levels between 4 and 5 micrograms per milliliter may be maintained. In an attempt to reduce the local irritating effect of oxytetracycline and tetracycline the commercially available vials of 100 mg. of powder when constituted to 2.0 ml. with distilled water or saline solution contain 50 mg. of magnesium hydrochloride per milliliter and 2 per cent procaine hydrochloride. The material should be injected into the gluteal muscle only and not into fat or subcutaneous tissue. Sensitivity to procaine should be determined prior to administration.

Intravenous preparations are available and should be restricted to those patients who are unable to take oral therapy because of vomiting or unconsciousness or for other reasons. These preparations may produce local thromboses of the vessels. High blood levels are achieved, and detectable serum concentrations may persist for as long as 24 hours. A single dose of 0.5 gm. of chlortetracycline given intravenously may reach a level of 10 micrograms per millimeter in three hours; 5 micrograms in six hours; 4 micrograms in nine hours; 2 micrograms in 12 hours; and 2 micrograms in 12 to 18 hours. After intravenous administration, chlortetracycline appears rapidly in the gastrointestinal tract. Adequate serum levels can be maintained by giving chlortetracycline intravenously at eight to 12 hour intervals in doses of 10 to 20 milligrams per kilogram per 24 hours. As soon as the patient can tolerate oral therapy, the intravenous administration should be discontinued.

Chlortetracycline passes from the blood into a variety of body fluids and can be found in the peritoneal fluid, cerebrospinal fluid, bile, urine and milk. Approximately 10 per cent of the ingested drug is not absorbed and is excreted in the feces. In patients with normal hepatic function the concentration of the tetracyclines in bile is from five to 15 times that noted in the serum. In pregnant women the tetracyclines pass into the fetal circulation through the placenta. According to Herrell, oxytetracycline does not transverse the blood-brain barrier as readily as chlortetracycline. However, in meningitis, oxytetracycline has been demonstrated in the cerebrospinal fluid. In a study made by Wood et al.[6] on the comparative ability of tetracyclines to reach the cerebrospinal fluid after intravenous administration, tetracycline appeared to give a higher cerebrospinal fluid level than oxytetracycline or chlortetracycline, after a single dose and more particularly when repeated doses were given. The levels of oxytetracycline seemed slightly higher than those of chlortetracycline. Because of the greater diffusability of tetracycline these authors suggested tetracycline as the drug of choice in the treatment of meningeal infections. The intravenous preparations have been given intrathecally in doses of 1 to 5 mg. This form of therapy should be used with extreme caution.

The tetracyclines are promptly excreted by the kidneys and can be found in peak concentrations in the urine from one to five hours after a single dose. In comparing the excretion of the three analogues Wright et al.[7] obtained similar results with individual variations. Approximately 10 to 20 per cent of the drug is excreted in the urine in the first 12 hours. The excretion may be prolonged with detectable concentrations noted four and five days after the discontinuation of the drug following multiple doses or after a large single dose. The maximum concentration reached is around 320 micrograms per milliliter and may be maintained for six to 12 hours. A large single oral dose of 1 gm. may approach this concentration; when larger doses are given, the drug appears in the feces. A single 0.5-gm. dose in an adult may result in a level of approximately 125 micrograms per milliliter in about three hours. The earlier studies comparing chlortetracycline and oxytetracycline indicated that considerably more oxytetracycline may be found in the urine and for a longer period with comparable doses. Perhaps the relative stability of oxytetracycline combined with the method of microbiological assay could in part account for this difference.

TOXICITY

The tetracyclines as a whole are of extremely low toxicity in man as well as in a wide variety of experimental animals. Children tolerate these agents better than do adults. The most recent analogue, tetracycline, produces the least number of objectionable complaints. Welch,[5] in considering the toxicity of chlortetracycline, compares an average daily dose of penicillin G of one million units or 0.6 gm. to high doses of chlortetracycline, such as 30 gm., which have been given orally without serious toxic reactions. Large intravenous daily doses of the tetracyclines in animals have been shown by Seto and Lepper[4] to produce an accumulation of fat in the liver, chlortetracycline being more active in this regard than the nonchlorinated analogues.

A great variety of untoward effects have been reported; some are due directly to the agent, and others result from a superimposed infection due to the emergence of tetracycline-resistant microorganisms or to the replacement of the normal flora. It is probable that a number of the early reports on the toxic manifestations of chlortetracycline were due to the presence of impurities in the early lots as well as to the use of extremely high doses. For the past number of years the chlortetracycline available for clinical use has been recrystallized three times. In spite of this, undesirable symptoms may occur, such as nausea, vomiting, anorexia, heartburn and epigastric distress. These may be considered local irritating symptoms because they do not occur after intravenous injection. Stomatitis, cheilosis, vaginitis, diarrhea and other

enteric symptoms such as flatulence and bulky, loose movements may result from an altered bacterial and fungal flora. Other oropharyngeal complaints such as black tongue, hoarseness, sore throat and a variety of eruptions in and around the mouth have been reported. A number of these lesions suggest vitamin B deficiency, and indeed a great deal of vitamin B complex has been used concurrently with the antibiotic, but without a striking relief in the symptoms. The withdrawal of the agent or the reduction in the dose has proved more effective. The addition of agents that have an inhibitory effect on candida and other fungi has been suggested. In some instances the clinical response appeared favorable.

The most serious effect is a fulminating gastroenteritis or pseudomembranous ileocolitis in which the predominant microorganism isolated from the stool is the Staphylococcus. Some patients were debilitated and chronically ill prior to the development of this complication, and the amount of antibiotic given was relatively high. However, a number of seriously ill patients with enterocolitis following tetracycline therapy recovered when early recognition of this complication was noted and prompt attention given to fluid balance and the use of erythromycin, which seems effective against the tetracycline-resistant Staphylococci. In recent years there appear to be fewer reports of this serious complication in spite of the more extensive use of these antibiotics. It occurs less often in children than in adults. The judicious use of the antibiotics, a better understanding of proper dosage and the early recognition of this complication should reduce the number of fatal cases.

In those patients who experience diarrhea following the first administration of the tetracyclines, repeat administration of the same agent should be done with caution. In our experience the occurrence of diarrhea following chlortetracycline and oxytetracycline in infants and children is relatively uncommon. In some patients, who are on therapeutic doses for prolonged periods, large, soft and more frequent stools may occur. In these instances the substitution of tetracycline for chlortetracycline has often resulted in an improvement in the number and consistency of the movements. The gastrointestinal symptoms are commonly noted in adults. As high as 30 per cent of adult patients may have nausea, diarrhea or other gastrointestinal complaints following administration of oxytetracycline. Approximately half this number have similar symptoms following administration of chlortetracycline. In the case of tetracycline this figure is close to 5 per cent.

Rarely encountered reactions have been observed in our hospital following chlortetracycline and oxytetracycline therapy. On a number of occasions, signs of increased intracranial pressure developed when small acutely ill infants suffering from respiratory infections were

treated with these antibiotics. Cerebrospinal fluid examinations were usually negative except for an increase in pressure. These acutely ill infants improved rapidly when the antibiotic was discontinued. A number of observers felt that the increased intracranial pressure was due to the antibiotic.*

It may be of interest to mention some of our observations made in the prolonged and continuous use of chlortetracycline and oxytetracycline in the treatment of patients with cystic fibrosis of the pancreas. The initial effect of therapeutic doses in these patients is an improvement of the pulmonary infection and a concomitant and striking improvement in the nutritional state of the patient. Phenomenal weight gains may occur in four to six weeks with doses as little as 10 mg. per kilogram per 24 hours. In 1949 we wondered whether this nutritional effect was due to some action of the chlortetracycline other than an antibiotic one. We still lack evidence to indicate that this is so. The remarkable effect of chlortetracycline and oxytetracycline on weight gain in animals is well known. The recent carefully controlled study of Jolliffe et al.[3] in Italian children does not point to the tetracyclines as having a specific growth effect in children who are inadequately fed.

In a group of over 300 infants and children treated continuously with chlortetracycline or oxytetracycline for periods of one year or more the number of undesirable reactions were few. The duration of therapy in some cases exceeded five years. The dose range was from 10 to 20 mg. per kilogram per 24 hours. Approximately 3 per cent required discontinuance because of diarrhea. Nausea and vomiting were rarely noted. Of special interest is the discoloration of the temporary teeth which we noted in approximately 5 per cent of patients. The entire tooth structure seems to be uniformly involved. The exact nature of the pigment or why this reaction should occur is unknown. To our knowledge this reaction has not been previously reported. Another uncommon type of reaction is that of photosensitivity. This occurred in approximately 3 per cent of our patients and was noted during the summer months when the children were exposed to the sun. Ready tanning of the skin and peeling were especially marked around the nose and face, although other exposed parts were affected. These same children in previous summers prior to the chlortetracycline and oxytetracyline therapy did not tan readily. The parents were aware of the striking difference during the periods off and on therapy. Tetracycline was substituted for chlortetracycline in two patients during the summer months, and the impression was gained that the photosensitivity reaction was averted.

* This experience was also encountered by Drs. John A. V. Davies, Donald Matson and William Berenberg.

REFERENCES

1. Chandler, C. A., and Bliss, E. A.: In Vitro Studies with Aureomycin. *Ann. New York Acad. Sc.*, 51:221, 1948.
2. Grove, D. C., and Randall, W. A.: *Assay Methods of Antibiotics. A Laboratory Manual*. New York, Medical Encyclopedia, Inc., 1955.
3. Jollife, N., and others: Effect of Aureomycin on Weight Gain of Italian Children Ages 6–10 on Diets Relatively Low in Animal Protein, in *Antibiotics Annual 1955–56*. New York, Medical Encyclopedia, Inc., to be published.
4. Seto, J. T., and Lepper, M. H.: The Effect of Chlortetracycline, Oxytetracycline and Tetracycline Administered Intravenously on Hepatic Fat Content. *Antibiotics & Chemother.*, 4:666, 1954.
5. Welch, H.: *Principles and Practice of Antibiotic Therapy*. New York, Medical Encyclopedia, Inc., 1954, p. 196.
6. Wood, W. S., Kipnis, G. P., and Dowling, H. F.: The Concentrations of Tetracycline, Chlortetracycline and Oxytetracycline in the Cerebrospinal Fluid after Intravenous Administration, in *Antibiotics Annual, 1953–54*. New York, Medical Encyclopedia, Inc., 1953.
7. Wright, S. S., and others: Clinical and Laboratory Observations on Tetracycline, in *Antibiotics Annual, 1953–54*. New York, Medical Encyclopedia, Inc., 1953, p. 92.

300 Longwood Avenue
Boston 15, Mass. (Dr. Schwachman)

ERYTHROMYCIN AND RELATED ANTIBIOTICS

Applied Pharmacology

EMITT H. SHOEMAKER, M.D.

ELLARD M. YOW, M.D.

The addition of the tetracyclines to the previously available antimicrobial agents provided physicians an armamentarium with which most infectious diseases could be controlled. There were notable exceptions to this success, however. Severe staphylococcal infections often did not respond to antibiotic therapy, and almost from the beginning of penicillin therapy an increasing number of infections have been due to staphylococci resistant to the antibiotics in use. The enterococci, which are a fairly common cause of bacterial endocarditis, have frequently been quite resistant to penicillin, making it necessary to give large doses in combinations with streptomycin, and even with this dosage regimen there have been treatment failures. The gram-negative bacilli have been responsible for an increasing number of infections and are frequent etiologic agents in secondary infections. Many strains of these organisms have been either natively resistant to many antibodies or have acquired resistance during therapy. Lastly, the complications of antibiotic therapy have frequently necessitated their withdrawal.

Because of these remaining therapeutic problems, research in the antibiotic field in recent years has been directed more specifically toward their solution. A large number of antibiotic substances have been studied, most of which have simply duplicated the effect of earlier antibiotics. Others have made a definite contribution largely because

From the Department of Internal Medicine, Baylor University College of Medicine, Houston, Texas.

of their activity against strains rather than species resistant to previously available agents. No completely safe antibiotics have yet been isolated which have the highly desirable bactericidal effect on all strains of the staphylococcus or the proteus and pseudomonas group of gram-negative bacilli.

It is the purpose of this paper to discuss the applied pharmacology of some of the newer antibiotics which have been found useful in the treatment of penicillin-resistant gram-positive infections and in treating patients in whom penicillin cannot be administered because of drug hypersensitivity.

ERYTHROMYCIN

Erythromycin was isolated by McGuire and colleagues[1,2] in the research laboratories of Eli Lilly in 1952. It was derived from a strain of *Streptomyces erythreus*. The soil sample which yielded this organism was collected in the Philippine Archipelago. Broth cultures contained a substance which was particularly active against gram-positive organisms, and was also reported to be active against gram-negative cocci and certain of the larger viruses.

Chemical and Physical Properties

Erythromycin is a basic compound. The pH of a saturated solution is approximately 9. It is soluble to the extent of 2 mg. per milliliter in water. It is extremely soluble in alcohols, acetone, ethyl acetate, chloroform and acetonitrile.

The crystalline material is bitter, white in color and stable at room temperature. Aqueous solutions at high and low concentrations are stable for eight weeks at 4° C. At room temperature there is some deterioration after seven to 10 weeks. Heating the material to 100° C. causes significant loss of activity in 15 minutes. Dilute solution may be filtered through Berkefeld filters with only slight loss of activity. Serum, sodium chloride, dextrose or reduced oxygen tension do not affect its activity. Of particular clinical significance is the fact that erythromycin is unstable in an acid medium and therefore must be protected from gastric juice.

This has been done by coating the tablets with an acid-resistant material and by preparing salts of erythromycin, such as erythromycin stearate or ethyl carbonate. These buffered salts are affected less by gastric juice and are so insoluble in water that only a slight bitter aftertaste is perceived after ingestion of the oral suspensions. Adequate absorption occurs after administration of either the coated tablets or the salts.

Antimicrobial Properties

The spectrum of erythromycin in vitro is similar to, but wider than, that of penicillin, though not so broad as that of the tetracyclines or chloramphenicol. In general, erythromycin is ineffective against the gram-negative bacilli. On a weight basis it is more active against the gram-positive organisms than is chloramphenicol or the tetracyclines. Virtually all strains of streptococci and staphylococci are inhibited by concentrations of 3.0 gammas per milliliter or less. Neisseria, Corynebacterium, Hemophilus and the clostridial organisms are also quite sensitive, and it is highly active against spirochetes.

Erythromycin exerts its effect only against multiplying bacteria. It is primarily bacteriostatic, but may be bactericidal when highly sensitive organisms are exposed to high concentrations. Naturally resistant variants among erythromycin-sensitive strains are rare. There is no cross resistance to other available antibiotics except carbomycin, to which there is almost complete cross resistance. Resistance to the antibiotic can be induced in vitro. The rate at which resistance develops varies with the strain of bacteria; staphylococci and enterococci develop resistance more rapidly than hemolytic streptococci or pneumococci. Resistance has also developed during erythromycin therapy of acute overwhelming staphylococcal septicemias. We have seen staphylococci develop significant resistance in vivo to erythromycin in 10 days when 3 gm. per day were being administered intravenously and 2 gm. orally. Just how frequently this occurs is not known.

There is some disagreement among authorities as to the rate and incidence of the development of resistance in population groups. Some investigators have suggested that erythromycin should never be given alone and should be used only in selected cases in order to prevent or delay the development of more and more resistant organisms in the general population. Other investigators have found only a slight increase in the number of resistant strains in hospital populations.

In the treatment of the individual patient acquired resistance is unlikely to be a problem unless the infection persists in the presence of therapy for a period of over a week. In overwhelming infections it may develop more rapidly. Resistance to erythromycin in vitro develops in a stepwise fashion at a rate similar to that observed with penicillin, not at the rapid rate seen with streptomycin.

Resistance can be markedly delayed by the simultaneous administration of another antibiotic to which the organism is also sensitive. There is no evidence that antibiotic antagonism is a problem in the clinical use of erythromycin.

Synergism with sulfadiazine has been demonstrated; with streptomycin, bacitracin and penicillin the combined effects are at least additive.

Absorption

Erythromycin is readily absorbed from the upper intestinal tract, but it must be protected from the action of acid gastric secretions. The current use of acid-resistant coated tablets or erythromycin salts has been effective in this regard and has resulted in higher and more consistent serum levels. Food in the stomach delays absorption, and achlorhydria has been reported to increase the amount of absorption.

After oral administration of erythromycin peak blood levels are attained at two hours and significant levels persist up to six hours. Larger doses result in higher blood levels. With a 250-mg. dose average peak levels of 1 to 2 micrograms per milliliter are attained. A single 500-mg. dose usually produces a serum concentration in two hours of 2 to 4 micrograms per milliliter. In patients with achlorohydria much higher concentrations, up to 20 to 30 micrograms per milliliter, are attained. These blood levels are usually adequate to inhibit most of the pathogenic susceptible organisms. In order to maintain adequate blood levels, it is necessary to administer the drug every four to six hours.

With the intravenous administration of 500 mg. of erythromycin over a 30 minute period higher blood levels are attained than after the same oral dose (7 to 30 mg. per milliliter at 15 minutes after completion of injection). There is, however, a more rapid decline in the blood level. Adequate doses by the intramuscular route are irritating, and it is our opinion that this route of administration will be infrequently indicated. In patients who are seriously ill requiring parenteral therapy the intravenous route is recommended.

Tissue Distribution

Erythromycin does not readily diffuse into the normal cerebrospinal fluid. With the usual dose administered only traces of the material can be detected. In patients with meningitis somewhat greater concentrations are attained. Low concentrations of the antibiotic have been demonstrated in brain tissue. Ascitic and pleural fluid levels are about 50 per cent as high as the blood level in patients on maintenance therapy.

Large amounts of erythromycin in active form are excreted in the urine and feces of patients on maintenance therapy. The biologically active material is concentrated in the liver and excreted in bile. Concentrations of 100 mg. per milliliter or greater are not unusual in bile of patients with T tube drainage of the common bile duct.

Indications for Use

Erythromycin is perhaps most useful as an alternative form of antibiotic therapy in the treatment of infections due to penicillin-resistant,

erythromycin-sensitive microorganisms. It is also used in the treatment of patients who are hypersensitive to penicillin. It is specifically indicated in the treatment of pneumococcal pneumonia when it is not desirable to administer penicillin. It is considered by Herrell to be as effective as penicillin in the treatment of this disease, and because of the lack of serious toxic manifestation it may be the agent of choice except in severe cases.

Because of its effectiveness against *Hemophilus influenzae*, the presence of these organisms in an infection should not create the problem in erythromycin therapy that has been observed in the administration of penicillin in children. Combined with bacitracin, erythromycin is the antibiotic of choice in the treatment of staphylococcal bacteremia until the results of antibiotic sensitivity tests are available. If sensitivity to penicillin is demonstrated, it then becomes the agent of

TABLE 6. *General Indications for Administration of Erythromycin*

1. Penicillin-resistant, erythromycin-sensitive gram-positive organisms, particularly infections due to staphylococci and nonhemolytic streptococci
2. Infections ordinarily treated with penicillin, but penicillin contraindicated because of drug hypersensitivity, such as hemolytic streptococcal infections
3. An oral form of therapy for diseases usually treated with penicillin, such as pneumococcal pneumonia
4. Indicated for its antibacterial effect in diphtheria

choice. If not, erythromycin combined with bacitracin, streptomycin, chloramphenicol or some other antibiotic to which the organism is also sensitive should be continued. Erythromycin is indicated in the treatment of other penicillin resistant staphylococcal infections such as ileocolitis, pneumonia, osteomyelitis and infections of the genitourinary tract. It is the antibiotic of choice in the treatment of diphtheria and diphtheria carriers. Antitoxin should of course be given in cases of diphtheria.

Erythromycin is indicated in the prophylaxis of rheumatic fever. It has been shown to be effective in doses as low as 200 mg. daily. The low incidence of bi-effects is a point in favor of its use over penicillin. The higher cost of erythromycin is a practical point against its use. Finally, it is indicated in diseases usually treated with penicillin, but in which an oral form of therapy is desirable.

During the past three years erythromycin has been used as a substitute for penicillin in the treatment of streptococcal endocarditis in approximately 20 patients seen in the hospital affiliated with Baylor University College of Medicine. When used alone, erythromycin has rarely been successful in permanently controlling the infection, but when combined with a bactericidal agent, such as streptomycin and bacitracin, it has been quite effective. This method of therapy is par-

ticularly useful in the case of penicillin hypersensitivity, and also obviates the painful problem of administering extremely large doses of penicillin to patients with the penicillin-resistant forms of enterococcal endocarditis.

Dosage and Mode of Administration

It is probable that the main reasons for treatment failures in the early clinical use of erythromycin were due to the administration of inadequate doses and inactivation of erythromycin by gastric juices of the material administered in gelatin capsules. With present day oral preparations and new dosages better results are being obtained.

TABLE 7. *Administration of Erythromycin**

SEVERITY OF INFECTION	CHILD	AVERAGE ADULT	COMMENT
Mild	25 mg./kg./day	1–1.5 gm./day	Divided in 4–6 doses
Moderate	30 mg./kg./day	1.5–2.0 gm./day	Divided in 4–6 doses
Severe	50 mg./kg./day	3.0 gm./day	Should be given intravenously initially

*These are oral doses, except as indicated. Erythromycin may be given intramuscularly as a supplement to oral or intravenous administration, but not usually as a substitute for either.

For the average adult with an infection of only moderate severity, 250 mg. every four to six hours are sufficient. With more severe infection 500 mg. every four to six hours are indicated. In a patient with bacteremia intermittent or continuous intravenous administration of erythromycin is indicated. The 24-hour dose by the intravenous route is 1.5 to 2 gm. The oral and parenteral dose for children is 30 to 50 mg. per kilogram per day divided into four to six doses. Because of the smaller total dosage used in pediatrics, intramuscular administration may be done in children weighing up to 25 kilograms. The larger doses necessary in larger persons cause too much local irritation at the site of injection to use it as a maintenance form of therapy. For parenteral use in such cases the intravenous route is recommended.

Preparations Available

Oral preparations are available in tablet, granule and liquid forms. Erythromycin stearate is supplied as a buffered salt of erythromycin in

100-mg. and 250-mg. tablets, and as an oral suspension containing 100 mg. per 5 ml. Erythromycin ethyl carbonate is also available as an oral suspension, 100 mg. per 5 ml. Erythromycin base is available in 100-, 200- and 250-mg. acid-resistant coated tablets. Both erythromycin base and erythromycin salts combined with triple sulfas are available in tablets, oral suspensions, and granules.

Preparations for Parenteral Use. Erythromycin Lactobionate and Erythromycin Glucoheptonate are available for intravenous use. The former is supplied in 30-cc. vials, containing the equivalent of 1 gm. of

TABLE 8. *Oral Preparations of Erythromycin for Systemic Use*

FORMS	CONCENTRATION OR SIZE	MANUFACTURER	TRADE NAME	COMMENTS
Tablets	100 mg., 250 mg.	Lilly	Ilotycin	Acid-resistant coated tablets
Tablets	100 mg., 250 mg.	Abbott	Erythrocin	Film-coated stearate salt
Tablets	100 mg., 200 mg.	Upjohn	Erythromycin	Coated tablets
Suspension	100 mg./5 cc.	Lilly	Ilotycin Pediatric	Ethyl carbonate salt
Suspension	100 mg./5 cc.	Abbott	Pediatric Erythrocin	Stearate salt
Granules	50 mg./packet	Upjohn	Erythrogran	Pediatric form
Drops	5 mg./drop	Lilly	Ilotycin Drops	Ethyl carbonate
Tablets	75 mg. plus 333 mg. sulfa	Abbott	Erythrocin with Sulfas	Stearate salt with triple sulfa
Tablets	75 mg. plus 333 mg. sulfa	Lilly	Ilotycin-Sulfa	Erythromycin base with triple sulfa
Tablets	100 mg. plus 249 mg. sulfa	Upjohn	Erythro-sulfa Tablets	Erythromycin triple sulfa form
Granules	50 mg. plus 500-mg. sulfas packets	Upjohn	Erythro-sulfa Granules	Pediatric form
Suspension	100 mg. plus 167 mg. sulfa/5 cc.	Lilly	Ilotycin-Sulfa	Pediatric form

erythromycin, and in 10-cc. vials, containing the equivalent of 300 mg. of erythromycin. The erythromycin Glucoheptonate is supplied in ampules containing an equivalent of 250, 500 and 1000 mg. of the base. Both preparations are supplied in dry form and are prepared for use by adding water for injection (USP) to the vials. This stock solution can then be added to 5 per cent dextrose or normal saline solution for intravenous infusion. This may be administered in a period of 30 minutes to as long as desired. Intramuscular preparations of erythromycin are also available. It has been our experience, however, that these cause too much local irritation at the site of injection to be of much clinical use. Erythromycin base for intramuscular use is supplied in 2- and 10-cc. ampules. The material comes ready for use and contains 50

mg. per milliliter. Erythromycin Lactobionate is used for both intravenous and intramuscular administration. The maximum concentration for intramuscular use should be 50 mg. per milliliter. It must be given deep in the muscle with no more than 100 mg. at each site. Most patients do not tolerate the intramuscular form for more than a few days.

Topical Use. Erythromycin and its salts are available for topical use. Ointments containing concentrations of 0.5 and 1.0 per cent are available. For ophthalmic use 0.5 per cent erythromycin and 1.0 per cent Erythromycin Lactobionate are available. Erythromycin 1 per cent has

TABLE 10. *Parenteral Forms of Erythromycin*

ROUTE OF ADMINISTRATION	FORM	CONCENTRATION	MANUFACTURER	TRADE NAME	COMMENTS
I.M.	Solution	50 mg./cc.	Lilly	Ilotycin I.M.	Erythromycin
I.M. and I.V.	Powder	0.3- & 1-gm. vials	Abbott	Erythromycin Lactobionate	Lactobionate salt
I.V.	Powder	0.25-, 0.5- and 1-gm. vials	Lilly	Ilotycin Glucoheptonate I.V.	Glucoheptonate salt

also been combined with neomycin 0.5 per cent for topical use. For otitic use 5 mg. of erythromycin with 10,000 units of polymyxin B per milliliter is available in 5 per cent benzocaine.

Toxicity and Side Effects

To date we are unaware of any severe bi-effects having been associated with the use of erythromycin. Indeed, it would appear that the low incidence of untoward reactions is one of the strong points in favor of the use of this antibiotic. The commonest side effects from the oral use are abdominal cramps, diarrhea, vomiting and nausea. With the usual dosage the incidence is low, but with 400- to 500-mg. doses the gastrointestinal side effects may create a problem in administration. They are a result of a direct irritating effect on the gastrointestinal tract and are not due to bacterial floral changes. They disappear within 24 to 48 hours after discontinuation of the drug.

Local sensitivity reactions to erythromycin ointments have been reported. Herrell has advised against its local use because of the development of hypersensitive reactions and the development of resistant organisms except in the rare instance in which other antibiotics have failed. As is true with other antibiotics, the wider use of erythromycin has been associated with the appearance of resistant strains of some bacteria, notably the staphylococcus.

The Problem of Erythromycin Resistance

Much can be done to prevent the emergence of resistant organisms to erythromycin. Adequate dosage to eliminate the infection as soon as possible is important in this regard. The simultaneous administration of another antimicrobial agent such as the sulfonamides or bacitracin to which the etiologic agent is also sensitive will delay the development of resistance. The avoidance of indiscriminate use of erythromycin, as with other antibiotics, will do much to prevent the widespread increase of resistant strains of microorganisms, particularly staphylococci.

OTHER RELATED ANTIBIOTICS

Many other antibiotic substances having a similar spectrum to that of erythromycin have been isolated. Among those studied clinically, two apparently identical antibiotics appear the most promising. These are streptonivicin (Albamycin), discovered in the Upjohn Research Laboratories, and cathomycin (Cathocin), isolated by Merck and blood levels attained. In Houston both have been tried clinically in a variety of conditions, including pneumococcal pneumonia, streptococcal pharyngitis, staphylococcal septicemia and mixed bacterial infections of the respiratory tract. The results have been similar to those seen with the use of penicillin in susceptible infections, and troublesome side effects have not been a problem. Also of interest are the preliminary observations of the effectiveness of these antibiotics in some urinary tract infections due to Proteus. This effect is enhanced by an acid pH. Early studies of their use in pertussis are also encouraging.

Other antibiotics that have received clinical trial include carbomycin, spiramycin and PA 105. Carbomycin (Magnamycin) is an antibiotic derived from *Streptomyces halstedii*. It was originally described as a new antibiotic by Tanner et al. in September, 1952. Since then it has been rather extensively investigated, both in the laboratory and clinically. It is a monobasic substance poorly soluble in water, but forms soluble salts with acids.

Its spectrum in vitro is essentially that of erythromycin. In fact, organisms made resistant to erythromycin are also resistant to carbomycin. On a weight basis it is less potent, is more toxic, and is not as rapid in action as erythromycin.

Blood levels following oral administration are low and are not comparable to those obtained with erythromycin. Rapid biliary excretion of carbomycin is said to account for the low serum levels. It does not diffuse into the cerebrospinal fluid. Clinically it has been used in a number of infections caused by susceptible organisms. The results have been satisfactory at times, but treatment failures are more common

than with erythromycin. At present it seems that carbomycin has no particular advantages over erythromycin, and it has certain disadvantages which erythromycin does not exhibit. It has, therefore, little or no place in antibiotic therapy.

Spiramycin was isolated from *Actinomyces streptomycin ambifaciens* by the French firm Rhone-Poulenc and is being studied in this country by Merck & Company. It is effective when administered orally primarily against gram-positive organisms. However, erythromycin-resistant species are usually also resistant to spiramycin.

PA 105 was isolated from *Streptomyces antibioticus* in the Pfizer Research Laboratories. It too exhibits cross resistance with erythromycin, though some strains of bacteria resistant to erythromycin are sensitive to PA 105.

SUMMARY

1. The resistance of certain microorganisms, notably the staphylococcus, to previously available antibiotics as well as the increasing number of complications associated with antibiotic therapy has stimulated the continued search for additional antimicrobial substances. The development of erythromycin has been one of the most promising outgrowths of this effort.

2. Erythromycin is active in vitro against most gram-positive organisms as well as many of the large viruses, rickettsiae and spirochetes. There is no cross resistance with other antibiotics.

3. Erythromycin has been most effective clinically against pneumococcal pneumonia, diphtheria, staphylococcal infections and streptococcal infections. One of its most important uses has been in the treatment of penicillin-resistant erythromycin-sensitive infections.

4. Resistance to erythromycin may develop during the therapy of severe staphylococcal septicemia, and there is some evidence that the incidence of erythromycin-resistant staphylococci is increased in the general population where the antibiotic is widely used. The development of resistance can be delayed by the combined use of other suppressive agents.

5. Presently available preparations are adequately absorbed when administered by the oral route. The dose may vary from 25 to 50 mg. per kilogram per day, depending upon the severity of the infection. Parenteral forms are available; however, the pain associated with the administration of the material intramuscularly limits its usefulness, and the intravenous route is preferable.

6. Undesirable side effects are rarely seen in association with erythromycin therapy. The most common are those resulting from its irritating effect on tissue, such as nausea, vomiting, diarrhea, abdominal cramps,

and pain at the site of injection. Skin rashes and drug fever have rarely been reported.

7. Other antibiotics with spectrums similar to that of erythromycin are being tried clinically. Most of these have shown no particular advantages over erythromycin, and cross resistance is frequently observed between erythromycin and carbomycin, spiromycin and PA 105. Cathomycin, however, does not exhibit this property and appears to be an antibiotic which will be useful clinically. The blood levels following the administration of equivalent doses of cathomycin are considerably higher than with erythromycin.

REFERENCES

1. Blute, J. F., Jr.: Use of Erythromycin in Diphtheria. *New England J. Med.*, 251:70, 1954.
2. Dearing, W. H., and Heilman, F. R.: Micrococcic (Staphylococcic) Enteritis as a Complication of Antibiotic Therapy; Its Response to Erythromycin. *Proc. Staff Meet., Mayo Clin.*, 28:121, 1953.
3. Gibson, C. D., Jr., Nushan, H., and Anderson, D. N.: The Treatment of Bacterial Pneumonia with Erythromycin: A Controlled Clinical Study. *Ann. Int. Med.*, 41:112, 1954.
4. Grigsby, M. E., and others: Erythromycin Sensitivity of Micrococcus Pyogenes Var. Aureus in a Hospital Population (Development of Resistance). *Antibiotics & Chemother.*, 5:350, 1955.
5. Haight, T. H., and Finland, M.: Antibacterial Action of Erythromycin. *Proc. Soc. Exper. Biol. & Med.*, 81:175, 1952.
6. Haight, T. H., and Finland, M.: Resistance of Bacteria to Erythromycin. *Proc. Soc. Exper. Biol. & Med.*, 81:183, 1952.
7. Haight, T. M., and Finland, M.: The Antibacterial Action of Erythromycin. *Proc. Soc. Exper. Biol. & Med.*, 81:175, 1952.
8. Haight, T. H., and Finland, M.: Laboratory and Clinical Studies on Erythromycin. *New England J. Med.*, 247:227, 1952.
9. Heilman, F. R., Herrell, W. E., Wellman, W. E., and Geraci, J. E.: Some Laboratory and Clinical Observations on a New Antibiotic, Erythromycin. *Proc. Staff Meet., Mayo Clin.*, 27:285, 1952.
10. Herrell, W. E.: *Erythromycin*. Antibiotics Monographs, No. 1. New York, Medical Encyclopedia, Inc., 1955.
11. Josselyn, L. E., and Sylvester, J. C.: Absorption of Erythromycin. *Antibiotics & Chemother.*, 3:63, 1953.
12. McGuire, J. H., and others: Ilotycin (Erythromycin-Lilly). *Antibiotics & Chemother.*, 2:281, 1952.

2920 Kirby Drive
Houston, Texas (Dr. Shoemaker)

CHLORAMPHENICOL

Applied Pharmacology

NATALIA S. FELIX, M.D.

Chloramphenicol (Chloromycetin), discovered in 1947,[12] is an antibiotic derived from *Streptomyces venezuelae*, a soil mold.[13] Later it was found that it is produced by a number of different species of Streptomyces.[7, 40] It can be produced by fermentation. It was the first antibiotic to be synthesized and to be successfully produced on a commercially practical basis in this manner.[27]

CHEMICAL AND PHYSICAL PROPERTIES

Chemically, chloramphenicol is a nitrobenzene compound and, like chlortetracycline (Aureomycin), contains nonionic chlorine.[33] It was the first aromatic nitro compound to be found in nature.

Chloramphenicol is a neutral crystalline compound occurring as fine white needle-like crystals or elongated plates.[3] It has a bitter taste. It is soluble in water to the extent of 2.5 mg. per milliliter at 25° C. Solubility in fats and oils is low. It is very soluble in the lower alcohols, propylene glycol, acetone and ethyl acetate; fairly soluble in diethyl ether; and insoluble in benzene and petroleum ether. The antibiotic is thermostable both in the dry condition and in solution. At room temperature it is stable in aqueous solution of pH 2 to 9 for at least 24 hours and unaffected in distilled water when heated to 37° C. for a month or when boiled for five hours or autoclaved for 30 minutes. It is rapidly inactivated in alkaline solution; more than 87 per cent is inactivated at pH 10.82 in 24 hours at 25° C. Solutions in water or in organic solvents darken slowly on exposure to light and, therefore,

From the Department of Pediatrics, Cedars of Lebanon Hospital, Los Angeles.

should be dispensed in amber-colored containers. The change in color is associated with loss of potency.[8]

ABSORPTION, DISTRIBUTION AND EXCRETION

The fate of chloramphenicol in the body has been extensively studied by Glazko et al.[16] It is rapidly absorbed, metabolized and excreted. Orally administered to man, it reaches its maximum blood concentration about two hours after a single oral dose with the height of the peak in direct proportion to the dose administered.[40] A dose of 0.5 gm. of the drug gives a peak plasma level of 4 micrograms per milliliter; a dose of 1 gm. gives 9 micrograms per milliliter, and so on. The close relation between the dose and plasma level of the drug is due to the rapid and almost complete absorption of the drug from the intestinal tract.

Although the blood levels obtained with chloramphenicol are higher than those obtained with oxytetracycline or chlortetracycline, the blood concentration of chloramphenicol falls more rapidly, so that by the sixth hour its concentration is somewhat lower than that obtained with similar doses of either oxytetracycline or chlortetracycline. The more rapid disappearance of the drug from the blood stream is due to the fact that it is rapidly metabolized, probably by the liver,[21] into an inactive nitro compound. Nevertheless, significant blood concentrations of chloramphenicol have been maintained for at least six to eight hours, and proper dosages at these intervals have been shown to be clinically effective.[40] Organisms sensitive to chloramphenicol are effectively suppressed by a blood concentration of 5 to 10 micrograms per milliliter.

Rectal absorption of the drug is a debated issue. Effective blood levels have been found by some, while unsatisfactory serum concentrations were found by others when perforated capsules of chloramphenicol were inserted into the rectum.[21]

Owing to the variables of hydration and utilization in severe infection, intramuscular administration of the drug may not result in blood concentrations uniformly consistent with the dose given. After intramuscular injection of single doses of 1 to 4 gm. or more of the drug in aqueous suspension, effective blood levels are maintained for 24 to 48 hours.[41]

Blood levels of chloramphenicol after intravenous administration as compared with those after equivalent oral doses were only slightly higher at three hours and only about twice as high after 12 to 24 hours.[6] A dose of 15 mg. per kilogram of body weight every six hours intravenously gave satisfactory blood levels for treating the majority of children having susceptible infections.[31]

High concentrations of chloramphenicol appear in the kidneys and liver, probably since these organs are active in excretion. After absorption it is widely distributed throughout all the tissues.[16, 18] It readily diffuses into all body fluids. Measureable concentrations may be found in the blood, urine, cerebrospinal fluid, pleural fluid, humor of the eye and other tissue fluids. The cerebrospinal fluid concentration of the drug is about 30 to 50 per cent of that in the blood. It also passes the placental barrier, reaching a concentration in the cord blood of 50 to 75 per cent of that found in the maternal blood.[34] It apparently also enters the intracellular compartments, since it is effective in the treatment of rickettsial infections.

The kidneys are the main route of excretion of chloramphenicol. About 90 per cent of the administered dose may be found in the urine in 24 hours. The bulk is in the form of an inactive nitro compound, and less than 10 per cent of the administered dose is excreted unchanged (biologically active form). The latter produces a sufficient concentration to be clinically effective in urinary infection. The biologically active form is largely excreted by glomerular filtration, while the inactive form is excreted mainly by tubular secretion. About 3 per cent of the administered dose is found in the bile. A negligible amount of the drug (about 1 per cent of the administered dose) is excreted in the stool in contrast to the tetracyclines, which are lost to a greater degree by the intestinal tract. As a result of this, chloramphenicol is less likely to cause diarrhea as compared with the tetracyclines or any of the poorly absorbed antimicrobial agents.[11]

ROUTES OF ADMINISTRATION AND DOSAGE

Chloramphenicol can be given orally, rectally, parenterally, topically and intrathecally.

Oral Route

Because of its exceedingly unpleasant bitter taste, the oral preparation of the drug is usually given in sealed hard gelatin capsules (Kapseals). The amount contained in each capsule is 50, 100 or 250 mg. However, in infants, children or occasionally adults who cannot swallow or have difficulty swallowing capsules, the drug has been given as a suspension using honey, black currant syrup, raspberry syrup, lemon syrup, syrup of Yerva Santa and other flavoring agents to mask the bitter taste. However, none of these preparations makes the crystalline drug really palatable.[8] The need for a more palatable oral liquid preparation of chloramphenicol led to the preparation of chloramphenicol

palmitate in a custard-flavored suspension (Pediatric Chloromycetin Palmitate Suspension) containing 125 mg. of chloromycetin base in 4 cc. This preparation is quite palatable. Chloramphenicol palmitate per se has no antibiotic properties, but upon hydrolysis of the palmitate ester by the intestinal lipolytic enzymes the antibiotically active chloramphenicol is liberated in the intestinal tract.[15, 42] Ross et al.[36] showed that chloramphenicol palmitate was hydrolyzed by all patients regardless of age or nature of illness—even in dehydrated infants or those with diarrhea or with cystic disease of the pancreas in which the pancreatic enzymes were inadequate. It is presumed that the lipases present in succus entericus are sufficient to hydrolyze the palmitic ester. The ester contains 57.6 per cent chloramphenicol base. Therefore, to achieve equivalent blood titers, a larger dose of palmitate than of the crystalline drug is required. Because of the gradual release of Chloromycetin from the palmitate, effective blood levels may be maintained longer with proper dosage of the ester compared to equivalent doses of crystalline chloramphenicol.[32]

Oral dosage of chloramphenicol in pediatrics using the crystalline preparation is 50 to 100 mg. per kilogram of body weight per day in divided doses. Using the chloromycetin palmitate suspension, the dosage is 100 to 150 mg. per kilogram of body weight per day in divided doses, according to Ross et al.[36] This is lower than that recommended by Mossberg,[29] who gives the palmitate in divided doses to a total of 200 mg. per kilogram per day.

Rectal Route

Chloramphenicol has been given rectally.[40] Rectal absorption of the drug, however, is still a debated issue. The capsule preparation of the drug is punctured and inserted rectally after a cleansing enema, and the buttocks are apposed for three to five minutes to assure retention. Suppositories of chloramphenicol (Alficetyn), an English preparation, are available, containing either 125 or 250 mg. of chloramphenicol in a base consisting essentially of cocoa butter.[8]

Intramuscular Route

Chloramphenicol can be given intramuscularly by using "Chloromycetin Intramuscular," which is available in "Steri-vials" containing 1 gm. of a specially prepared microcrystalline form suspended in an aqueous vehicle. Because of the repository quality of "Chloromycetin Intramuscular," an adult dosage schedule of 1 gm. given every eight to 12 hours has been effective in severe infections. The dosage schedule

for children weighing 15 kilograms or less is 100 to 150 mg. per kilogram of body weight per day, usually divided into two doses at 12 hour intervals. Heavier children should receive 1 gm. every 12 hours.

Intravenous Route

Intravenous injection of chloramphenicol is intended as a temporary emergency measure for those patients unable to take oral preparations. It should be discontinued in favor of the oral route as soon as the patient's condition permits. The current available intravenous preparation of the drug is called "Chloromycetin Solution." It is supplied in 2-cc. ampules containing 500 mg. of chloramphenicol in a 50 per cent aqueous solution of N,N-dimethylacetamide. This solution is intended primarily for intravenous use and must be diluted according to directions. The contents of each 500-mg. ampule should be diluted at room temperature in at least 100 cc., but not more than 250 cc., of the sterile diluent, such as physiologic salt solution or dextrose solution. The concentrated "Chloromycetin Solution" should be withdrawn from the ampule with a dry syringe and needle and should be added under the surface of the diluent. Note that *"Chloromycetin Solution" as supplied should always be added to the diluent; reversing this procedure or failing to add the solution beneath the surface of the diluent may result in precipitation of chloramphenicol.* It is preferable to insert the needle through the rubber diaphragm of an upturned intravenous flask. The usual rate of injection is 2 to 5 cc. per minute of the prepared solution, and it should never exceed 20 cc. per minute. This preparation in the undiluted form is also suitable for intramuscular injection, but only if given deeply into the gluteal muscles. The adult dose of intravenous chloramphenicol is 0.5 to 1 gm. every six to 12 hours (approximately 7 to 15 mg. per kilogram of body weight). The dosage for infants and children is 15 to 20 mg. per kilogram of body weight every six hours.

Topical

The preparations for topical use are the "Chloromycetin Cream, 1 per cent"; "Chloromycetin Ophthalmic ointment, 1 per cent"; Chloromycetin Ophthalmic"; "Chloromycetin-Hydrocortisone Ophthalmic"; "Chloromycetin Otic," containing 0.5 per cent chloramphenicol and 1 per cent benzocaine in propylene glycol; and "Chloromycetin Topical," which is a 50 per cent solution in propylene glycol. These preparations are intended for topical use for skin, eye and ear infections.

Other Routes

Chloramphenicol has been used subcutaneously as a 0.25 per cent solution with hyaluronidase. Satisfactory blood levels have been reported.[20]

It has also been used intrathecally with excellent results in cases of staphylococcal meningitis resistant to penicillin and streptomycin.[2]

UNTOWARD REACTIONS

Review of the literature has shown that the great majority of investigators who have used this drug clinically have reported no untoward reactions. Occasionally, however, undesirable side effects with the use of chloramphenicol, like other antibiotics, have been reported. They are in the form of dermatologic, systemic and miscellaneous reactions. Among the systemic manifestations are those involving gastrointestinal, neurologic, liver and, most significant, the hematopoietic system.

Dermatologic

Urticaria, eczematoid dermatitis, contact dermatitis or maculopapular eruptions may occur. These lesions are infrequent.[1]

Hematopoietic[23, 26, 31]

In 1950, the year following the clinical use of chloramphenicol to any extent, cases of bone marrow depression were first reported. These and subsequent reports led to the conduction of a special nationwide survey of the possible deleterious effects of chloramphenicol on the bone marrow. The incidence of aplastic anemia following chloramphenicol administration was estimated to be 1 in 40,000 patients receiving the drug. There was no constant relation between the bone marrow depression and the dose, duration of therapy or allergic diathesis of the patient. Depression of the marrow was found to occur following the use of other drugs such as sulfonamides, oth[illegible] broad-spectrum antibiotics, anticonvulsants, antihistamines and antipyretics. All ages were affected. Distribution of sex showed a predominance of females over males by almost 3:1 and infrequently involving Negro patients.

As a result of this survey Lewis et al.[26] of the Food and Drug Administration concluded that in certain susceptible patients chloramphenicol may cause blood dyscrasia, including aplastic anemia, thrombocytopenic purpura, granulocytopenic purpura, granulocytopenia and

ancytopenia. However, it cannot be stated categorically that the incidence of blood dyscrasias has increased since chloramphenicol became available, because the figures in the group who had received chloramphenicol and in the group that did not receive it paralleled each other closely.

The development of blood dyscrasias due to this drug has been a rare occurrence. Many thousands of patients who have received the drug did not have ill effect.[4, 10] However, despite the rare occurrence of this complication, the U.S. Food and Drug Administration has recommended that it should not be used indiscriminately or for minor infections and that adequate blood studies be carried out when prolonged or intermittent administration is required.

The nitrobenzene radical has been incriminated by some authors as the myelotoxic agent responsible for these dyscrasias. Most probably a sensitivity mechanism is the most important factor which would explain the blood dyscrasias even after minimal doses or repeated courses of the drug.[21]

Gastrointestinal

There are reports of gastrointestinal disturbances like nausea, vomiting and diarrhea due to chloramphenicol, but these disturbances are not as marked as those caused by the tetracyclines. Pseudomembranous colitis has been reported.[1] Altered sense of taste,[40] glossitis, stomatitis, sore throat, proctitis, pruritus vulvae, pruritus ani and sprue syndrome have been reported.[28]

The change in the intestinal flora following extended use of the drug has been ascribed by some to be the cause of these gastrointestinal manifestations. This change is in the form of overgrowth of nonsusceptible organisms, especially *Candida albicans*, with a concomitant decrease in susceptible flora. There have been reports of bronchomoniliasis, mycotic endocarditis and meningitis. In children the development of clinical thrush or other forms of moniliasis seems to depend on the duration of treatment, dosage and the presence of *C. albicans* before treatment. The development of moniliasis as a result of the use of this drug in therapeutic doses does not seem likely if it is administered for not more than eight days.[28]

Neurologic

Peripheral neuritis of the lower extremities associated with bilateral optic neuritis,[1, 23, 25] depression with tearfulness,[2] headache and dizziness[19, 21] have been reported.

Liver Involvement

Acute necrosis of the liver following chloramphenicol therapy has been reported.[23, 37]

Miscellaneous

Anaphylactic shock,[21] mild Jarisch-Herxheimer reaction,[40] and some irritation at the site of injection have been reported.

ANTIMICROBIAL ACTIVITY

Chloramphenicol is one of the broad-spectrum antibiotics with marked antimicrobial activity against a wide variety of pathogenic organisms,[40] including the rickettsiae, certain strains of viruses like those causing lymphogranuloma venereum, primary atypical pneumonia, psittacosis, trachoma, mumps[14] and granuloma inguinale, certain bacilli, staphylococci, streptococci, gonococci, pneumococci, brucellae, certain Salmonellae, including *Eberthella typhosa*,[17] some spirochetes like the *Treponema pallidum* and *pertenue* and many strains of both gram-negative and gram-positive microorganisms which have become resistant to the effects of other antibiotics.

The effect of chloramphenicol upon sensitive organisms is primarily bacteriostatic. The inhibitory effects of this drug on the bacterial esterase system may be a clue to the mechanism of its antibacterial properties.[38]

Emergence of resistant strains to chloramphenicol is infrequent and, if encountered, is of low grade as compared with other antibiotics. However, one should keep this in mind when therapeutic response of a chloramphenicol-sensitive organism is unsatisfactory; re-evaluation of the sensitivity of the organism may reveal the development of resistance.[21]

CLINICAL INDICATIONS

Chloramphenicol is effective in a number of clinical conditions, including septicemia, meningitis,[22] urinary tract infections, brucellosis, bacterial and primary atypical pneumonias, pertussis, enteric fevers, including typhoid fever, dysenteries due to Shigella infections,[24, 35] infections due to *Hemophilus influenzae* bacilli, and other systemic infections and local infections due to susceptible organisms. Local application of the drug is indicated when susceptible organisms are found in wounds, burns, dermatoses,[30] mucous membrane lesions, osteomyelitis and eye or ear infections.

Its effectiveness in typhoid fever is outstanding and unequaled by that of any other known antibiotic.[9, 40]

An important prophylactic use of chloramphenicol lies in its bacteriostatic effect on the intestinal flora, making it possible to reduce or eliminate certain pathogens prior to surgical procedure. It has been used in the prevention and cure of septic peritonitis and in the prevention of infections that may arise in other parts of the body as complications of colon surgery.[5] It has also been used in prophylaxis of infantile gastroenteritis.[39]

Chloramphenicol is useful in urinary tract mixed infections caused by gram-negative and gram-positive organisms resistant to other antibiotics. Sensitivity of many strains of pathogens to chloramphenicol and limited tendency of these organisms to develop resistance to this antibiotic explain the effectiveness of chloramphenicol where other antibiotics and chemotherapeutic agents have failed.

SUMMARY

Applied pharmacology of chloramphenicol in infants and children has been discussed, mentioning the source of the agent, its chemical and physical properties, absorption, distribution and excretion, routes of administration and dosage forms of the drug, untoward reactions, antimicrobial activity and clinical indications.

REFERENCES

1. Alexander, H. L.: Anti-infectious Drugs (Antibiotic Preparations): Chloramphenicol (Chloromycetin), in *Reactions with Drug Therapy*. Philadelphia, W. B. Saunders Company, 1955, Chap. VI, pp. 103–105.
2. Anderson, K. F., and Ellis, F. G.: Intrathecal Chloramphenicol in Staphylococcal Meningitis Resistant to Penicillin and Streptomycin. *Brit. M.J.*, 2:1067, 1951.
3. Bartz, Q. R.: Isolation and Characterization of Chloromycetin. *J. Biol. Chem.*, 172:445, 1948.
4. Bercovitz, Z. T.: Chloramphenicol in Chronic Ulcerative Colitis: Clinical Results and Blood Counts over a 4½ Year Period in 67 Patients, and Sensitivity Studies of Predominating Organisms in Stools, in *Antibiotics Annal.* New York, Medical Encyclopedia, Inc., 1953–54, pp. 261–67.
5. Boling, E., and Finch, H.: Value of Chloromycetin in Colonic Surgery. *Am. Surgeon*, 18:903, 1952.
6. Burnell, J. M., and Kirby, W. M. M.: Serum Concentrations of Chloramphenicol Following Intravenous and Intramuscular Administration. *J. Lab. & Clin. Med.*, 38:234, 1951.
7. Carter, H. E., Gottlieb, D., and Anderson, H. W.: Chloromycetin and Streptothricin. *Science*, 107:113, 1948.
8. Council of the Pharmaceutical Society of Great Britain: *Antibiotics: A Survey of Their Properties and Uses*. 2nd ed. London, Pharmaceutical Press, 1952.
9. Dowling, H. F., Jackson, G. G., Kagan, B. M., and Lepper, M. H.: Problems in Antibiotic Therapy. Panel discussion. *Chicago M. Soc. Bull.*, July, 1955.
10. Doyle, J., Bell, D., Ross, S., and Rice, E. C.: Bone Marrow and Peripheral Blood

Study of Infants and Children Receiving Antibiotic Therapy, with Particular Reference to Chloramphenicol. *Clin. Proc. Child. Hosp.*, 10:87, 1954.

11. Drill, V. A.: Chemotherapy of Bacterial Infections: Chloramphenicol (Chloromycetin), in *Pharmacology in Medicine*. New York, McGraw-Hill Book Company, Inc., 1954, Chap. 79, pp. 1–3.
12. Ehrlich, J., Bartz, Q. R., Smith, R. M., Joslyn, D. A., and Burkholder, P. R.: Chloromycetin, a New Antibiotic from a Soil Actinomycete. *Science*, 106: 417, 1947.
13. Ehrlich, J., Gottlieb, D., Burkholder, P. R., Anderson, L. E., and Pridham, T. G.: Streptomyces Venezuelae, N. Sp., the Source of Chloromycetin. *J. Bact.*, 56: 467, 1948.
14. Ghalioungui, P.: Chloramphenicol in Mumps. *Lancet*, 2:75, 1950.
15. Glazko, A. J., Edgerton, W. H., Dill, W. A., and Lenz, W. R.: Chloromycetin Palmitate, a Synthetic Ester of Chloromycetin. *Federation Proc.*, 11:55, 1952.
16. Glazko, A. J., Wolf, L. M., Dill, W. A., and Bratton, A. C., Jr.: Biochemical Studies on Chloramphenicol (Chloromycetin). II. Tissue Distribution and Excretion Studies. *J. Pharmacol. & Exper. Therap.*, 96:445, 1949.
17. Greengard, J., Breslow, L., and Milzer, A.: Treatment of Typhoid in Children with Chloramphenicol (Chloromycetin). *Am. J. Dis. Child.*, 81:636, 1951.
18. Gruhzit, O. M., Fisken, R. A., Reutner, T. F., and Martino, E.: Chloramphenicol (Chloromycetin), an Antibiotic: Pharmacological and Pathological Studies in Animals. *J. Clin. Investigation*, 28:943, 1949.
19. Hansbery, J. W.: Present Concepts in the Treatment of Purulent Meningitis. *Neurology*, 4:301, 1954.
20. Harrell, G. T., Jr.: Treatment of Rocky Mountain Spotted Fever with Antibiotics. Presented as Symposium on Use of Antibiotics in Tropical Diseases, New York Academy of Science, January, 1952.
21. Hussar, A. E., and Holley, H. L.: Chloramphenicol, in *Antibiotics and Antibiotic Therapy: A Clinical Manual*. New York, Macmillan Company, 1954, Part II, pp. 144–50; Part III, pp. 235–38.
22. Kagan, B. M.: Current Status of Antimicrobial Agents in Pediatrics. *J.M.A. Georgia*, May, 1955.
23. Kagan, B. M., and Faller, L.: Untoward Reactions to Antibiotics. *M. Clin. North America*, 39:111, 1955.
24. Kunstadter, R. H., Milzer, A., and Kagan, B. M.: Chloramphenicol and Terramycin in the Treatment of Salmonella and Shigella Infections. *J. Pediat.*, 39: 687, 1951.
25. Lasky, M. A., Pincus, M. H., and Katlan, N. R.: Bilateral Optic Neuritis Following Chloramphenicol Therapy. *J.A.M.A.*, 151:1403, 1953.
26. Lewis, C. N., Putnam, L. E., Hendricks, F. D., Kerlan, I., and Welch, H.: Chloramphenicol (Chloromycetin) in Relation to Blood Dyscrasias, with Observations on Other Drugs: A Special Survey. *Antibiotics & Chemother.*, 2:601, 1952.
27. Long, L. M., and Troutman, H. D.: Chloramphenicol (Chloromycetin). VII. Synthesis through p-Nitroacetophenone. *J. Am. Chem. Soc.*, 71:2473, 1949.
28. McGovern, J. J., and others: The Effect of Aureomycin and Chloramphenicol on the Fungal and Bacterial Flora of Children. *New England J. Med.*, 248:397, 1953.
29. Mossberg, H.: The Dosage of Chloromycetin Palmitate in Children. *Acta paediat.*, 43:174, 1954.
30. Newman, B. S., and Feldman, F. F.: Treatment of Pyogenic Dermatoses with Topical Application of Chloramphenicol (Chloromycetin). *A.M.A. Arch. Dermat. & Syph.*, 64:212, 1951.
31. Orr, W. W., Preisser, W. C., Ross, S., Burke, F. G., and Rice, E. C.: Evaluation of Intravenous Chloramphenicol. A Preliminary Report. *Antibiotics & Chemother.*, 1:63, 1951.
32. Pratt, R., and Dufrenoy, J.: Chloromycetin, Aureomycin and Terramycin, in

Antibiotics. 2nd ed. Philadelphia, J. B. Lippincott Company, 1953, Chap. X, pp. 195–204.

33. Rebstock, M. C., Crooks, H. M., Jr., Controulis, J., and Bartz, Q. R.: Chloramphenicol (Chloromycetin). IV. Chemical Studies. *J. Am. Chem. Soc.*, 71:2458, 1949.
34. Ross, S., Bischoff, H., Preisser, W., and Orr, W. W.: Some Observations on the Absorption and Excretion of Aureomycin and Chloramphenicol. *J. Clin. Investigation*, 28:1050, 1949.
35. Ross, S., Burke, F. G., Rice, E. C., Washington, J. A., and Stevens, S.: Chloramphenicol (Chloromycetin) Therapy in Shigella Enteritis. *J.A.M.A.*, 143: 459, 1950.
36. Ross, S., Burke, F. G., and Rice, E. C.: The Use of Chloromycetin Palmitate in Infants and Children: A Preliminary Report. *Antibiotics & Chemother.*, 2: 199, 1952.
37. Salm, R.: Acute Necrosis of Liver Following Chloramphenicol Therapy. *Edinburgh M.J.*, 60:334, 1953.
38. Smith, G. N., Worrel, C. S., and Swanson, A. L.: Inhibition of Bacterial Esterases by Chloramphenicol (Chloromycetin). *J. Bact.*, 58:803, 1949.
39. Todd, R. M., and Hall, E. G.: Chloramphenicol in Prophylaxis of Infantile Gastroenteritis. *Brit. M.J.*, 1:1359, 1953.
40. Welch, H.: Chloramphenicol, in *Principles and Practice of Antibiotic Therapy*. New York, Medical Encyclopedia, Inc., 1954, Chap. IX, pp. 21–24, 205–229.
41. Welch, H., and Lewis, C. N.: Chloramphenicol, in *Antibiotic Therapy*. Washington, D.C., Arundel Press, Inc., 1951, p. 184.
42. Yow, E. M., Taylor, F. M., Hirsch, J., Frankel, R. A., and Carnes, H. E.: Chloromycetin Palmitate. *J. Pediat.*, 42:151, 1953.

4833 Fountain Avenue
Los Angeles 29, California

POLYMYXIN, NEOMYCIN AND BACITRACIN

Applied Pharmacology

ERNEST JAWETZ, M.D.

The peptide antibiotics polymyxin B, neomycin and bacitracin occupy a special place in the chemotherapeutic armamentarium. They claim no "general usefulness," "broad spectrum" or "first choice in any infection," as do so many other widely advertised antibiotics. On the contrary, it is generally accepted that these drugs should be used with restraint and only upon specific indication. If used improperly, all these substances can produce toxic side effects.

Because of their toxic potentialities they have been used only to a limited extent in medical practice. As a result, microbial resistance to these drugs has not developed on a large scale, as has been the case with more widely used antibiotics. Thus this group of agents has assumed increased usefulness in the control of certain infections with microorganisms resistant to the "common" antibiotics.

POLYMYXIN

Three independent research organizations announced in 1947 the discovery of antibiotic substances produced by *Bacillus polymyxa* (*B. aerosporus*), a soil organism. The polymyxins (A, B, C, D, E) are a group of basic polypeptides with a molecular weight of about 1100. They contain various amino acids in addition to a C_9 fatty acid (d-6-methyloctan-1-oic acid). Polymyxins are stable as acid salts, even

Based on work supported, in part, by grants from Burroughs, Wellcome and Co.; the Council on Chemistry and Pharmacy, American Medical Association; the National Institutes of Health (E 214); and Charles Pfizer and Co.

in solution, for long periods. The infra-red absorption spectrums of individual polymyxins are characteristic.

Because of excessive nephrotoxicity the use of polymyxin A, C and D has been abandoned. Only polymyxin B and E are presently used in clinical medicine. In the United States polymyxin B is used exclusively (N.N.R. 1954). It contains the amino acids leucine, phenylalanine, threonine and α, γ-diaminobutyric acid. Commercial preparations of polymyxin B are 65 to 75 per cent pure. They form white or yellowish scales which are readily soluble in water or physiologic saline solution up to concentrations of 25 milligrams per milliliter. The unit of polymyxin B is based on a theoretical potency of 10,000 units per milligram of the pure drug. Thus 1 microgram equals 10 units. The drug is distributed in terms of "equivalent weight" of the pure material, in dry form.

Antimicrobial Activity

Polymyxin B is a highly selective antimicrobial substance specifically active against gram-negative rods. Especially against *Pseudomonas aeruginosa* polymyxin is more effective by weight than any other antibiotic. Most strains of this organism are inhibited by 8 micrograms per milliliter or less.* Many coliform bacilli and shigellae are likewise highly susceptible. Proteus species are often resistant.

Polymyxin is a strongly bactericidal substance which acts by disturbing the osmotic equilibrium of the bacterial cell with which it establishes contact. This markedly increases the permeability of the cell wall so that cellular constituents, particularly purines and pyrimidines, escape into the environment. With a few bacteria actual lysis can be observed.

Resistance to polymyxin develops slowly in most microbial species. However, occasional resistant strains may be encountered among usually susceptible microbial species. There is no cross resistance with other clinically used antibiotics. On the contrary, it has been observed that certain microorganisms which are subcultured in subinhibitory concentrations of tetracyclines or chloramphenicol acquire increasing resistance to the drug to which they have been exposed, but at the same time become more susceptible to the action of polymyxin B. The clinical application of this phenomenon is uncertain.

Combinations of polymyxin with other drugs have been widely used, particularly because of its limited spectrum. When a wide range of microorganisms must be affected, e.g., in suppressing the intestinal flora

* Quantitative tube sensitivity tests are often essential in polymyxin therapy because disk sensitivity tests are unreliable. Polymyxin B diffuses poorly into agar and therefore gives exceedingly narrow zones of inhibition around disks, even with highly sensitive bacteria.

or in mixed surface infections of skin or mucous membranes, polymyxin B is administered together with other drugs acting principally on gram-positive bacteria. In these instances polymyxin does not interact with the other component of the drug mixture, but each agent acts on a separate portion of the microbial population.

Polymyxin can also participate in combined antibiotic action which results in true drug potentiation or synergism against a single microbial species. This synergism has been observed most frequently with streptomycin, tetracyclines or chloramphenicol against coliform organisms, Salmonellae and occasionally Proteus. Such synergistic action makes possible the use of small safe doses of polymyxin for long periods in conjunction with other drugs, whereas, alone, such small amounts of polymyxin might be inadequate for therapy.[4]

Toxicity

When applied topically to skin, mucous membranes, granulating or denuded surfaces, polymyxin B is virtually nonirritating and little absorbed if concentrations of 1 mg. per milliliter or gram are used. Similarly it is poorly absorbed and virtually nontoxic when given by mouth in doses of 20 mg. per kilogram per day or less. When polymyxin is administered parenterally, the toxic side effects are well defined and fall into the following categories.

Local Pain at the Site of Injection. This differs markedly with individual lots. After intramuscular injection there is transient local pain for a short time, comparable to the discomfort encountered with the injection of similar fluid volumes of other substances. However, about 40 to 70 minutes after the injection a "drawing," "aching" pain sensation returns and lasts from one to eight hours, often radiating peripherally in the sensory nerve distribution. There is great variation among patients and unpredictable differences from day to day in the same person. This local pain is much less pronounced in children than in adults. Its mechanism is not clear. It can be partially prevented or diminished by mixing the polymyxin with 1 per cent procaine hydrochloride or other local anesthetic.

Neurotoxicity. Neurotoxicity manifests itself in two forms, depending on the route of administration. After intramuscular injection of doses which result in serum levels of polymyxin B in excess of 1 or 2 micrograms per milliliter there is commonly flushing of the face, dizziness progressing with increasing dosage to demonstrable ataxia, drowsiness, and a variety of paresthesias and hypesthesias. Most regular among these are paresthesias of the circumoral and stocking-glove distributions. All these side effects tend to be milder in children than in adults, and always disappear completely within 24 to 72 hours after discon-

tinuing the drug. Sequelae are never encountered. Some of these side effects, particularly flushing of the face and various skin rashes, can occasionally be relieved by antihistaminics.

The intrathecal injection of polymyxin B in daily doses of 5 mg. or less is not usually accompanied by symptoms suggesting direct irritation of meninges or nervous tissue. With higher doses (5 to 10 mg. daily), however, there may be transient meningeal irritation with headache, stiff neck, pleocytosis and increased protein content of the cerebrospinal fluid, and fever. All these disappear soon. Doses greater than 10 mg. per day should never be injected intrathecally because they may produce serious side effects in the central nervous system.

Nephrotoxicity. With proper attention and knowledge the nephrotoxic effects of polymyxin B should never prevent the use of the drug when it is indicated in patients with reasonably good renal function. At parenteral dosage levels of 2.5 mg. per kilogram per day or more, there frequently develops proteinuria, cylindruria, and an increase in white, red and epithelial cells in the urinary sediment. With doses above 3 mg. per kilogram per day nitrogen retention frequently develops and the glomerular filtration rate diminishes. These disturbances of renal function tend to increase with the duration of polymyxin administration. However, they are reversible if treatment is short. There is never any indication for the use of such large doses. In patients with pre-existing normal renal function the administration of 2.2 mg. per kilogram per day or less for two weeks is not accompanied by significant nephrotoxicity.

In patients with pre-existing significant impairment of renal function much greater caution is necessary because in them doses of 1.5 mg. per kilogram per day of polymyxin, or even less, may result in additional depression of kidney function. Such patients should receive parenteral polymyxin only if good laboratory control of renal function is available, and their dose should be limited to 1 to 1.5 mg. per kilogram per day for five to 10 days.

Other Side Effects. Fever, itching of the skin and a variety of rashes occur occasionally and always disappear promptly when the parenteral drug is discontinued. Allergic sensitization appears to be rare. Gastrointestinal disturbances, e.g., nausea, vomiting and anorexia, are rare with oral doses of 20 mg. per kilogram per day or less.

Absorption, Distribution and Excretion

After oral administration of 20 mg. per kilogram per day or topical application of preparations containing 0.1 per cent polymyxin B, there is no significant absorption and no drug can be found in blood or urine.

When administered as aerosol, polymyxin B is absorbed to a slight extent.[6]

After intramuscular injection of 2 mg. per kilogram per day the drug is slowly absorbed, resulting in serum levels of 1 to 5 micrograms per milliliter. It is distributed unequally in the body: parenchymatous organs are reached by blood-borne polymyxin, but polymyxin does not readily pass from the blood stream into body cavities (e.g., pleural or joint spaces) or into the central nervous system and the cerebrospinal fluid. In order to achieve therapeutically effective concentrations in the appropriate location, the drug has to be injected intrathecally, intra-articularly or intrapleurally.

Though polymyxin diffuses adequately into many body tissues, its therapeutic activity is often limited in parenchymatous organs because the drug appears to combine with tissue constituents, particularly polyphosphates. Thus bacteria lodged in tissues often remain unaffected.

After parenteral administration polymyxin is excreted largely in the urine. Up to 60 per cent of the administered drug has been recovered, and urine levels as high as 10 to 160 micrograms per milliliter have been encountered.

Administration and Dosage

Intramuscular Injection. Polymyxin B is available as a sterile powder in 50-mg. amounts in multiple-dose vials. For injection the material is dissolved by adding 1 ml. of sterile isotonic salt solution and 0.5 ml. of 1 per cent procaine solution. After the powder has been completely dissolved appropriate amounts of the solution are injected deeply into the upper outer quadrant of the gluteal muscle. The solution is stable and may be kept in the refrigerator for several days.

Intramuscular injection is indicated in systemic infections with bacteremia and in urinary tract infections due to *Pseudomonas aeruginosa* or other gram-negative rods shown by laboratory test to be highly susceptible to polymyxin and relatively resistant to other antimicrobial agents. In serious infections with *Pseudomonas aeruginosa* polymyxin B may be presumed to be the drug of choice and administration begun before laboratory tests have been completed. In patients with relatively normal renal function the intramuscular daily dose should be limited to 2.5 mg. per kilogram. In those with pre-existing kidney impairment it should be limited to 1.5 mg. per kilogram per day and treatment carefully followed by frequent laboratory checks on some measure of nitrogen retention. The daily dose is usually administered in three or four equal injections (i.e., every six to eight hours).

Intrathecal Injection. In meningitis due to *Pseudomonas aeruginosa* and occasionally other gram-negative bacteria which are resistant to other antibiotics, intrathecal administration of polymyxin B is the treatment of choice. The sterile powder is dissolved in saline solution to give final concentrations of 0.5 mg. per milliliter. Procaine must *not* be added. The dose for children under two years is 2 mg. daily; for older children, 5 mg. After daily injections for three to seven days the drug may be administered every other day in the same dose for the remainder of three weeks, or for at least one week after the sugar content of the cerebrospinal fluid has returned to normal and all cultures have been negative.

Oral Administration. Scored tablets containing 50 mg. of polymyxin B are available. Other preparations contain smaller doses of polymyxin B together with other antimicrobial drugs. These oral preparations are used either for the preoperative preparation of the bowel or for susceptible bacterial infections limited to the intestinal tract, e.g., shigellosis. The daily dose is 10 to 20 mg. per kilogram.

Topical Administration. Solutions or ointments containing approximately 1 mg. per milliliter or gram of polymyxin B can be applied to infected surface lesions of skin or mucous membranes, wounds and burns, particularly if *Pseudomonas aeruginosa* is present in large numbers. Many different dosage forms are available, all of which take advantage of the fact that high concentrations of polymyxin B are stable and poorly absorbed and have great antibacterial effectiveness against gram-negative organisms with which intimate contact can be established.

Clinical Use

Polymyxin is most effective as a therapeutic agent when it can be brought into direct contact with susceptible, gram-negative organisms at the site of their multiplication, without having to pass tissue barriers. Thus it is well suited for the treatment of infections caused by susceptible bacteria which are limited to surfaces such as mucous membranes of the eye and intestine, skin lesions, wounds, infected burns or body spaces, e.g., pleural cavity, joint space or dural sac. Bacteremias due to susceptible organisms, without involvement of deep tissues, may respond because high blood levels can be achieved with the intramuscular injection of polymyxin. Because polymyxin is excreted in the urine in high concentration, it is suitable for the suppression of sensitive organisms causing urinary tract infections.

Among the infectious microorganisms which are susceptible to polymyxin, *Pseudomonas aeruginosa* occupies a special place. Not only is it

resistant to most other antibiotics, but also it tends to cause infectious processes relatively limited by tissue barriers and generally fails to invade parenchymatous organs. Thus it is singularly well suited to therapy by polymyxin. Although Pseudomonas is often called an "opportunist" rather than a primary pathogen, it may cause disease marked by chronicity, severity and even significant mortality unless it is adequately treated.[2]

In the following clinical situations polymyxin B has been used successfully:

Pyelonephritis in Children. Polymyxin is useful in acute pyelonephritis particularly when following some urologic manipulation which introduced Pseudomonas into the urinary tract. Full systemic doses (2.0 to 2.5 mg. per kilogram per day) should be injected intramuscularly for seven to 10 days. This treatment often not only suppresses the symptoms of pyelonephritis promptly, but also eradicates the organisms from the kidney before they have an opportunity to establish a chronic infection. In chronic pyelonephritis due to susceptible bacteria, polymyxin may likewise suppress symptoms, but rarely eliminates the chronic focus of infection in the interstitial tissue of the kidney. Nevertheless polymyxin therapy is occasionally rewarding because it may make the patient feel well for long periods.

Bacterial Meningitis. In bacterial meningitis due to *Pseudomonas aeruginosa* and occasionally other gram-negative bacilli (e.g., coliform bacilli which are resistant to other drugs) treatment must always be based on an etiologic diagnosis with isolation of the organism in the laboratory and examination for its sensitivity to the drug. Since polymyxin B does not diffuse to any extent from the blood stream into the cerebrospinal fluid, intrathecal injection is essential, and simultaneous intramuscular injection is often unnecessary. The daily intrathecal dose should not exceed 5 mg. for children over two years and 2 mg. in smaller infants. This dose should be administered in a concentration not exceeding 0.5 mg. per milliliter daily for three to seven days, and on alternate days for the remainder of three weeks.

With such doses there are usually no side effects, or at most transient headache, fever, and pleocytosis of the cerebrospinal fluid. Cerebrospinal fluid levels of 0.5 to 5.0 micrograms per milliliter can be reached.

Chronic Shigellosis. For most intestinal infections, including acute shigellosis, polymyxin B is not the treatment of choice. However, in chronic shigella infection, either with symptomatic relapses of dysentery or merely as the asymptomatic carrier stage, polymyxin B, 15 to 20 mg. per kilogram per day given for 10 to 15 days, can eradicate the organisms from the intestinal tract more effectively than other drugs.[7]

In small infants *Pseudomonas aeruginosa* occasionally is associated with diarrhea and enterocolitis.[9, 10] Oral polymyxin B can eliminate the organism and control the symptoms in such cases. Since polymyxin B affects only gram-negative organisms, it has to be administered together with other drugs for effective suppression of the intestinal flora prior to operation. Combinations of polymyxin B, 15 mg. per kilogram per day, with bacitracin, 2000 units per kilogram per day, or neomycin, 20 mg. per kilogram per day, for 48 hours effect rapid and relatively complete suppression of the intestinal flora without side effects.[2, 12]

Superficial Infections of Skin, Mucous Membranes, Eye, Ear. These usually are associated with a mixed bacterial flora which can be effectively suppressed by combinations of polymyxin B with other drugs. A multitude of preparations are available for this purpose. Wounds and sinuses infected with *Pseudomonas aeruginosa* often respond to irrigation or wet dressing with solutions containing 1 mg. per milliliter of polymyxin B.

Systemic Infections. Many systemic infections due to invasive gram-negative bacilli (e.g., Salmonella, brucella, pasteurella) fail to respond to treatment with polymyxin B. However, bacteremias with noninvasive bacilli (such as may accompany the preceding conditions in infants) frequently respond promptly to full systemic doses of polymyxin B.

NEOMYCIN

Waksman and Lechevalier[11] in 1949 described a soil organism, *Streptomyces fradiae,* which produced a new antimicrobial substance. Later it became clear that the antimicrobial substances elaborated by this microorganism form a mixture which contains an antifungal agent, fradicin ($C_{30}H_{54}N_4O_4$), in addition to a "neomycin complex" which has antibacterial but no antifungal properties. The "neomycin complex" consists of three components, neomycins A, B and C, which are present in varying proportions in different preparations of the drug. The isolation and purification of these components presented great difficulties. The components can be distinguished to some extent by their relative inhibitory activity on different test organisms and by their optical properties.

Neomycin is a basic material which readily forms salts with a variety of acids. In the dry state these salts are stable. Commercial neomycin contains at least 90 per cent neomycin B. The present neomycin B sulfate standard is founded on the pure base with a theoretical potency of 1000 micrograms per milligram of material. When expressed in terms of units, each milligram contains 333 units (1 unit equals 3 micrograms).

Antimicrobial Activity

Neomycin possesses significant activity in vitro against a variety of gram-positive, gram-negative and acid-fast microorganisms, but not against most yeasts, fungi and true viruses. Many microbial species are inhibited by 5 to 10 micrograms per milliliter or less of neomycin; most important from a therapeutic standpoint, staphylococci (including penicillin- and tetracycline-resistant strains) and proteus are often susceptible.

Resistant bacterial strains are not infrequently encountered among susceptible species. However, resistant variants emerge relatively slowly under conditions of clinical therapy. Cross resistance with streptomycin has been observed. Neomycin acts predominantly as a bactericidal substance. It is occasionally synergistic with such other bactericidal drugs as penicillin or bacitracin when acting on a single microbial species. When used together with other drugs (e.g., sulfonamides, tetracyclines, polymyxin B) against a mixed bacterial flora, neomycin and its companion drug act on separate parts of the flora, and the two drugs do not interact with each other.

Toxicity

The parenteral use of neomycin is limited by its significant neurotoxicity and nephrotoxicity. A multitude of toxic effects have been observed in experimental animals, varying with species and dose, but the outstanding toxic side effects in man are a sudden onset of permanent deafness and some impairment of renal function. The loss of hearing is commonly partial rather than complete and may develop as late as one to two weeks after the drug has been discontinued. Its onset and development are unpredictable. It occurs without premonitory signs, but generally only if the drug has been injected in doses exceeding 15 mg. per kilogram daily for one week. There appear to be significant differences both in the toxicity of different lots of the drug and in the individual susceptibility of the patient.

The toxic action of neomycin on the kidney includes the production of proteinuria, cylindruria and hematuria, and nitrogen retention leading to uremia in extreme cases. Nitrogen retention occurs particularly in patients with pre-existing impairment of renal function. Patients with known kidney disease should therefore receive neomycin only under close clinical and laboratory surveillance. In persons with normal renal function parenteral neomycin administration often leads to proteinuria, but if the dose does not exceed 15 mg. daily for one week, significant nitrogen retention rarely develops.

After oral administration neomycin is absorbed poorly, and toxic

side effects are therefore rare. When applied topically to skin or mucous membranes, neomycin is relatively nonirritating, not highly sensitizing, and so little absorbed that systemic toxicity need not be considered.

Absorption and Excretion

Upon topical administration of less than 0.5 gm. to skin or mucous membranes, little, if any, neomycin is absorbed, so that none can be demonstrated in blood or urine. After oral administration the bulk is excreted in the feces, not more than 3 per cent of the total dose has been recovered in the urine, and little has been found in blood or tissue.[1] After intramuscular injection, neomycin is readily absorbed and distributed to body fluids and tissues. With intramuscular doses of 10 to 15 mg. per kilogram per day, serum levels of 10 to 30 micrograms per milliliter can be attained in two or three days. They remain stable at that level thereafter, except in patients with impaired renal function, in whom the concentration may rapidly rise. The drug is excreted principally through the kidneys, up to 50 per cent of the dose being recovered in the urine. Urine levels may reach from 100 to 1000 micrograms per milliliter and may continue for 24 hours after drug administration has been discontinued.

Administration and Dosage

Intramuscular Administration. For injection, neomycin sulfate is available as a sterile powder in multiple-dose vials, to be dissolved in physiologic salt solution. It should be used only in severe systemic infections in which neomycin is shown by laboratory test to be far more effective than other drugs. The daily dose should not exceed 15 mg. per kilogram per day, and preferably be limited to 10 mg. per kilogram per day, to be injected intramuscularly in four to six divided doses. In most cases the treatment should be limited to one week.

Oral Administration. Scored tablets of 0.5 gm. are available, as well as tablets containing varying amounts of neomycin together with other drugs, particularly bacitracin and polymyxin B. The oral route is rarely indicated for gastrointestinal infections. It is used most commonly for the preoperative preparation of the gastrointestinal tract for surgical procedures on the large bowel. Neomycin can be used alone for this purpose in doses of 100 mg. per kilogram per day, but this may occasionally permit the absorption of sufficient drug to result in toxic side effects. It is preferable to give only 20 mg. per kilogram per day of neomycin in combination with other poorly absorbed antibiotics (e.g., bacitracin, 2000 units per kilogram per day) or sulfonamides,

100 mg. per kilogram per day. Such combinations suppress the large bowel flora effectively.

Topical Administration. Neomycin may be applied to skin, mucous membranes, wounds and superficial infections, or may be injected intrapleurally or intra-articularly in the form of a sterile solution containing 5 mg. per milliliter. Commonly the drug is incorporated into an ointment base in a concentration of 5 mg. per gram, together with other antibiotics or cortisone. Such ointments are used for mixed infections of the skin or eye, in the hope of suppressing a complex bacterial flora and inhibiting the inflammatory response. The rationale for the widespread use of these ointments is often dubious and their effect uncertain, but they enjoy great popularity.

Clinical Use

In many systemic diseases neomycin should not be used, because the risk of its use outweighs the probable beneficial effects and because other more efficient and less toxic drugs are generally available. Whenever the parenteral use of neomycin is contemplated, the etiologic microorganism must have been isolated and its sensitivity determined. Only if the organism is inhibited by less than 10 micrograms per milliliter of neomycin, and if other drugs appear far less effective, should neomycin be injected intramuscularly.

In doses of 10 mg. per kilogram per day, neomycin has been useful in the following clinical situations in children: (1) blood stream infections in infants due to staphylococci, Proteus or other gram-negative bacilli which are resistant to other available antimicrobial drugs; (2) urinary tract infections, particularly acute pyelonephritis due to the same organisms.

Oral administration of neomycin has been used for the following purposes: (1) For rapid preoperative preparation of the bowel, neomycin can either be given alone in a dose of 100 mg. per kilogram per day or, preferably, 20 mg. per kilogram per day, together with bacitracin, 2000 units per kilogram per day, or polymyxin B, 20 mg. per kilogram per day, or tetracycline, 20 mg. per kilogram per day by mouth. The drugs are given for 48 hours before operation so that a maximal suppression of intestinal flora may be expected at the time of operation.[3] (2) In bacterial intestinal infections neomycin, 100 mg. per kilogram per day, may be effective, particularly in infant diarrhea due to certain serotypes of *E. coli*, *Proteus morgagnii* or paracolon bacteria.

Topical administration of neomycin as solution or ointment (5 mg. per milliliter or gram) is highly effective in pyogenic dermatoses and

infected eczema in children. Similar ointments have been applied to cases of conjunctivitis of presumed bacterial origin.

BACITRACIN

Johnson, Anker and Meleney[5] in 1943 isolated a strain of *Bacillus subtilis* from the wound of a patient named Tracy. This organism produced an antibiotic substance which they named bacitracin.

At present bacitracin is made by the deep-tank fermentation process. The unit of bacitracin in the United States is equivalent to 26 micrograms of the Food and Drug Administration working standard. Commercial bacitracin is produced to give fairly uniform potencies between 40 and 50 units per milligram. The material is approximately 80 per cent pure. Higher purification results in marked instability.

Commercial bacitracin is a white or buff-colored neutral substance readily soluble in water, poorly in alcohols. In the dry state it is stable for many months at 20° C., but loses potency rapidly at 75° C. In solutions of pH 5 to 7 bacitracin is stable for four weeks at 4° C., but at alkaline pH it is inactivated rapidly. Zinc bacitracin and bacitracin methylene disalicylate are relatively insoluble salts which are more stable than bacitracin in the dry state.

Chemically, bacitracin is a polypeptide consisting of at least five components. The principal one, called bacitracin A, has a molecular weight near 1470 and yields upon hydrolysis a mixture of amino acids including l-leucine, l-isoleucine, l-cystine, l-histidine, l-lysine, d-phenylalanine, d-ornithine, d-glutamic acid and dl-aspartic acid.

Antimicrobial Activity

Bacitracin has selective activity against gram-positive organisms and spirochetes, but is largely inactive against gram-negative rods. Susceptible organisms are generally inhibited by 0.005 to 2.0 units per milliliter in broth and include many strains of staphylococci, clostridia and other gram-positive cocci and rods. The action of bacitracin is predominantly bactericidal. Resistance to bacitracin does not emerge rapidly. However, resistant strains are encountered in many susceptible species of bacteria. There is no significant cross resistance with other antibiotics.

Bacitracin occasionally enters into true synergistic combinations with other antibiotics, particularly penicillin and streptomycin. This action has been particularly important in the treatment of systemic staphylococcal infections. However, more commonly bacitracin is administered together with other antibiotics in an effort to cover a "broad spectrum" of infectious organisms. Since bacitracin acts selectively on gram-posi-

tive bacteria, it is usually combined with drugs acting on gram-negative organisms, e.g., polymyxin B, neomycin or tetracyclines. With such drug combinations each of the drugs present affects a separate part of the microbial flora, and no combined antibiotic effect is involved.

Toxicity

The outstanding undesirable side action of bacitracin is its nephrotoxicity, which limits severely the dose and time of its administration. This manifests itself as proteinuria, hematuria and nitrogen retention. The degree of nephrotoxic action depends on the amount of bacitracin absorbed daily and the time of its administration. With oral and topical application, bacitracin is so little absorbed that there is virtually no danger of toxicity. With intramuscular injection of therapeutic doses of about 1000 units per kilogram per day there usually develops proteinuria and hematuria after a few days. These disappear promptly when the drug is discontinued, and nitrogen retention usually does not develop. However, when drug accumulates, either because higher doses are injected or because the patient is incapable of excreting the drug through a poorly functioning kidney, nitrogen retention may become significant and in extreme cases lead to uremia. Thus it is essential that all patients with known impairment of renal function be followed closely with suitable laboratory tests to guard against serious nitrogen retention during bacitracin therapy. Serious nephrotoxicity has been observed in a number of adults receiving average doses of bacitracin, but it has not yet been reported in children. In the vast majority of instances, doses of 1000 units per kilogram per day are tolerated reasonably well for at least two weeks, with only slight and transient proteinuria, hematuria, cylindruria and minimal depression of glomerular and tubular function.

Among other side effects of bacitracin there may be pain, petechial hemorrhages and induration at the site of intramuscular injection, a variety of skin rashes, tinnitus and minor gastrointestinal disturbances.

When administered orally in doses of 2000 units per kilogram per day or topically in concentrations of 1000 units per milliliter, bacitracin is not irritating to most tissues. It does not readily induce hypersensitivity.

Absorption, Distribution and Excretion

After oral or topical administration, absorption is poor and no significant blood or tissue levels result. After intramuscular injection, bacitracin is readily absorbed, producing blood and tissue levels which reach from 0.3 to 3.0 units per milliliter with doses of 1000 units per

kilogram per day administered for several days. Intramuscularly injected bacitracin reaches pleural and ascitic fluid, but does not occur in the cerebrospinal fluid in significant concentration.[13]

Parenterally administered bacitracin is excreted mainly by way of the urine. Orally administered bacitracin is excreted in the feces.

Administration and Dosage

Intramuscular Injection. Bacitracin is available as a sterile powder packaged in sealed vials in quantities not exceeding 60,000 units. The material is dissolved in sterile physiologic salt solution to give a concentration of 10,000 units per milliliter, and enough procaine hydrochloride is added to give a final concentration of 0.5 per cent. The total daily dose should not exceed 1200 units per kilogram, and preferably be limited to 1000 units, to be injected in four equal amounts deeply into the gluteal or deltoid muscle. During parenteral bacitracin therapy adequate fluid intake must be maintained to result in an ample urine volume. Laboratory tests for the detection of nitrogen retention must be carried out frequently. Extreme caution is necessary when parenteral bacitracin is administered to patients with pre-existing renal damage.

This form of therapy is indicated only in serious infections caused by antibiotic-resistant, bacitracin-sensitive bacteria, particularly staphylococci.

Intrathecal Injection. Experience with this form of administration is limited. Doses from 1000 to 10,000 units daily have been given in meningitis or brain abscess caused by staphylococci.

Oral Administration. Bacitracin in doses of 500 to 2000 units per kilogram per day can be given together with other poorly absorbed antibiotics to suppress the intestinal flora for preoperative preparation. (See Polymyxin B.)

Topical Application. Bacitracin enjoys its greatest popularity in the area of topical therapy. A long list of ointments, solutions, troches and tablets is available. The concentration of bacitracin in such preparations ranges from 100 to 1000 units per milliliter or gram. Commonly, bacitracin is combined with other drugs which act on gram-negative bacteria. Such combined preparations are useful in the pyogenic dermatoses and other superficial bacterial mixed infections.

Clinical Use

Bacitracin has no place in the treatment of a large majority of clinical infections. It finds its greatest usefulness in the therapy of serious infections due to gram-positive organisms resistant to other antibiotics, especially staphylococci; in surgical infections; and in topical therapy

of superficial infections of skin and mucous membranes. Bacitracin has been applied successfully to the following clinical situations:

Infections Due to Penicillin- and Tetracycline-Resistant Staphylococci, Including Bacteremias, Bacterial Endocarditis, Osteomyelitis, Empyema, Lung Abscess and Central Nervous System Infections. Treatment consists of full systemic doses of 1000 units per kilogram per day injected intramuscularly, and often combined with a second antibiotic, e.g., penicillin or streptomycin, when laboratory tests indicate possible synergistic effects of the combination. Whenever possible, drainage of suppurating areas must be instituted (e.g., abscess empyema, osteomyelitis), and topical bacitracin, 1000 units per milliliter, applied.

Surgical Infections Associated with a Mixed Bacterial Flora. Meleney et al.[8] reviewed the extensive experience of several investigators and concluded that a majority of surgical infections, both superficial and deep, respond to bacitracin therapy.

Mixed Infections of Skin, Eye or External Ear. These frequently respond to topical therapy with a combination of bacitracin and other antibiotics in the form of a multitude of available proprietary preparations.

Preoperative Use. Oral bacitracin, 2000 units per kilogram per day, may be used together with other drugs for preoperative preparation of the bowel. (See Polymyxin.)

REFERENCES

1. A.M.A. Council on Pharmacy and Chemistry: Neomycin Sulfate. *J.A.M.A.*, 154:338, 1954.
2. Jawetz, E.: Infections with *Pseudomonas Aeruginosa* Treated with Polymyxin B. *Arch. Int. Med.*, 89:90, 1952.
3. Jawetz, E., and Bierman, H. R.: Suppression of the Intestinal Flora in Man by Means of Mixtures of Poorly Absorbed Antibiotics. *Gastroenterol.*, 21:139, 1952.
4. Jawetz, E., Coleman, V., and Gunnison, J. B.: The Participation of Polymyxin B in Combined Antibiotic Action. *Ann. Int. Med.*, 41:79, 1954.
5. Johnson, B. A., Anker, H., and Meleney, F. L.: Bacitracin: A New Antibiotic Produced by a Member of the *B. Subtilis* Group. *Science*, 102:376, 1945.
6. Kagan, B. M., Krevsky, D., Milzer, A., and Locke, M.: Polymyxin B and Polymyxin E. *J. Lab. & Clin. Med.*, 37:402, 1951.
7. Lieberman, D., and Jawetz, E.: Treatment of Chronic *Shigella* Infection in Children with Oral Polymyxins. *Pediatrics*, 8:249, 1951.
8. Meleney, F. L., and others: The Efficacy and the Safety of the Intramuscular Administration of Bacitracin in Various Types of Surgical and Certain Medical Infections; With an Analysis of 270 Cases. *Surg., Gynec. & Obst.*, 89:657, 1949.
9. Mills, G. Y., and Kagan, B. M.: Effect of Oral Polymyxin B on *Pseudomonas Aeruginosa* in the Gastrointestinal Tract. *Ann. Int. Med.*, 40:26, 1954.
10. Waksman, S. A., and Lechevalier, H. A.: Neomycin, a New Antibiotic Active against Streptomycin-Resistant Bacteria, Including Tuberculosis Organisms. *Science*, 109:305, 1949.

11. Walker, S. H.: Polymyxin B in *Pseudomonas* and Proteus Enteritis. *J. Pediat.*, 41:176, 1952.
12. Welch, H., Randall, W. A., and Price, C. W.: The Effect of Streptomycin-Bacitracin-Polymyxin Combination, Polymyxin B and Streptomycin with Glucuronolactone on the Intestinal Flora of Man. *J. Am. Pharm. A.*, 34:486, 1950.
13. Zintel, H. A., Ma, R. A., Nichols, A. C., and Ellis, H.: The Absorption, Distribution, Excretion and Toxicity of Bacitracin in Man. *Am. J. M. Sc.*, 218: 439, 1949.

University of California Medical Center
San Francisco 22, California

COMBINATIONS OF ANTIMICROBIAL AGENTS IN PEDIATRIC PRACTICE

FREDERICK C. FINK, PH.D.

J. W. STRODE, M.D.

Despite the profound inroads against infectious diseases made possible during the past two decades by the introduction of the sulfonamides and a variety of antibiotics, many problems in the treatment and prevention of infectious diseases remain. Some species of pathogenic bacteria have been found generally resistant to all available antimicrobial agents—at least to all individual agents given singly. Others that were usually amenable to newly introduced agents have presented the problem of an increasing incidence of resistant strains consequent to the extensive use of those agents.

In addition to the search for new agents, investigations aimed at a solution to these remaining and growing problems have increasingly in the past few years been focused on the potentialities of antimicrobial combinations.

Antimicrobial combinations have a clear-cut application, of course, in mixed infections with components not covered by a single broad-spectrum agent. Possible indications in this category include peritonitis resulting from perforation of an abdominal viscus, bronchiectasis, lung abscess, otitis media (if the tympanic membrane has ruptured), urinary tract infections, infected wounds and mixed infections of body cavities. The agents selected for therapy should be those likely to be most effective against each component of the infection considered separately.

On occasion, microbial populations of a single species are probably not homogeneous in their responsiveness. By giving two drugs, each of which affects differing strains, it may be possible to obtain a more complete over-all effect.

Combinations may be advisable also as initial therapy, while laboratory studies are being made, in serious infections in which the identity

of the causative organism is not apparent or in which all possible efforts to obtain a rapidly bactericidal action cannot be delayed.

THE PROBLEM OF EMERGENT RESISTANCE

Fortunately, the microorganisms responsible for most acute infections (pneumococci, meningococci, gonococci, group A beta hemolytic streptococci, spirochetes, rickettsiae) have shown no tendency toward development of resistance to the antibiotic agents. On the other hand, there is an increasing number of microorganisms—the staphylococcus in particular—that possess or can develop means of resisting these agents. The discovery of a way to halt this trend of increasing resistance represents a real challenge. The introduction of newer antimicrobial agents with the ability to interfere with the adaptive processes of microorganisms in such a way as to preclude the development of drug resistance offers the best hope of solving this problem. Until this is realized, however, we should not overlook the possible utility of the now available agents administered in various combinations.

In a recent review of the genetic aspects of the development of bacterial resistance to antimicrobial agents, Wright, Boyer and Strode[25] point out that antimicrobial therapy with a single drug sometimes fails because drug-resistant mutants emerge early in therapy. The addition of a second agent may prevent this development of early drug-fastness. The inhibition by one drug of the rapid emergence of forms resistant to the second drug is undoubtedly an important mechanism of combined drug action and should prove of considerable clinical significance. The application of this principle is limited by the patterns of resistance to different drugs and cross resistance among them. Thus drugs between which there is cross resistance (i.e., tetracycline-chlortetracycline-oxytetracycline or erythromycin-carbomycin)[20, 22] cannot be usefully given together. Some such mixtures, however, may have pharmacologic utility in diminishing toxicity at a given level of antimicrobial effectiveness (e.g., streptomycin plus dihydrostreptomycin).

In the treatment of tuberculosis this principle of preventing drug resistance by combined therapy is well established. One agent with a high antimicrobial activity (streptomycin or isoniazid) is used in combination with a second having a lower activity (para-aminosalicylic acid), but a different pattern of microbial resistance, thus preventing early emergence of mutants resistant to the first agent. Much longer profitable therapy is thereby made possible.

Staphylococcal Resistance

Numerous studies have shown that the main problem of resistant staphylococci is one that concerns hospitalized patients.[1, 5, 10, 15, 16, 19]

The pattern of resistance here develops more slowly than is seen in tuberculosis, it involves larger populations of pathogens, and it is not restricted to the body of a single patient. It is characterized by a gradual increase in resistant strains in a given hospital, usually over a period of months or years, and it is associated with the widespread use of a given drug. When use of that drug is discontinued, strains resistant to it diminish only gradually. This type of resistance does not result from emergence of resistant mutants in each clinical case, but from the gradual accumulation of mutants maintained in a reservoir population of microorganisms about the hospital.

The introduction of penicillin and other antibiotics has been followed by a gradual increase in staphylococci resistant to each of them. Resistance develops slowly in stepwise increments through several mutations. Thus its development requires a large population in which successive mutants can accumulate in quantity in preparation for each succeeding mutation. This is evident on considering the extremely low incidence of mutation in each gene.[25] A resistant cell differing from a sensitive cell by only three gene mutations would require a reservoir population of 10^{18} cells to produce at the rate of once per cell generation. Populations that approach such astronomical size and are constantly exposed to chemotherapeutic agents are found only in hospitals where such agents are used on a large scale.

The fact that many such resistant populations disappear only slowly when the drug is discontinued indicates that they are not only well adapted in the presence of the drug, but also can compete with their sensitive fellows in the absence of the drug.

Thus hospital populations of staphylococci are a double hazard: They are a source of infections refractory to agents in use at the hospital, and they are a potential source of permanently drug-resistant strains that would never appear in the absence of the large reservoir population necessary for their evolution.

Effort must be directed toward preventing the origin of resistant strains; once they are present, their adaptive advantage is highest precisely when therapy is used against them.

Because the rate of production of resistant mutants is a function of population size, the only effective method of preventing their origin is to reduce the size of the population and to minimize its growth. Since the source of the difficulty lies not in each patient, but in hospital populations, attempts might well be made to eliminate these populations, to reduce their size, or to render them ineffective as sources of cross infection.

Any degree of isolation of patients would tend to limit the population size of pathogens to that within each patient. Such populations are not of the magnitude necessary for the formation of multiple

mutants in a finite length of time. Further, the absence of interchange of organisms between patients and the hospital reservoir carries with it the encouraging possibility that resistant organisms might permanently disappear, since the reservoir would no longer be exposed to new sources of resistant organisms and to selection by antibiotics. Any practices that result in separating patients from sources of hospital infection will tend to reduce the danger of resistant infection. Thus there may well be occasion in antimicrobial therapy for considering the application of communicable disease practices.

Other practices in antimicrobial therapy that might be considered are a period of disuse for each of the widely used antibiotics, thus allowing resistance to diminish in hospital reservoirs; withholding one effective agent from general use and reserving it for treatment of infections resistant to other agents; practicing greater economy in the use of antimicrobial agents, not only by restricting their use to cases in which they are specially indicated, but also by giving them in sufficient amounts to achieve a complete effect in the shortest possible time; avoiding agents that allow rapid emergence of resistance; avoiding the use of antibiotics for treatment of trivial infections and for prevention of infections which there is little need to fear and those which, if they arose, could probably be controlled quite easily; and treating a larger proportion of infections in the home.

Little information is available concerning the use of antimicrobial combinations in a hospital population with a view to reducing the actual incidence of transfer of resistant strains. If a combination of drugs is used from the beginning, and there are few if any organisms resistant to either, and these few organisms are resistant to only one of the drugs but not to both, then the use of an effective combination of drugs in hospitalized patients should reduce markedly the problem of transfer between personnel and patients.

MANAGEMENT OF RESISTANT INFECTIONS

The problem of management is not one of treating organisms, but of treating patients with infections caused by such organisms.[13] This may be difficult and require full knowledge and skill in the use of antimicrobials. Most of the recent interest in antimicrobial combinations has stemmed from the possibility of their usefulness against infections caused by microorganisms not amenable to any antimicrobial agents used individually.[2-5, 11-14] Pseudomonas and Proteus, except for occasional strains, have never been affected by any individual agent thus far available; and the most frequent causative organisms of bacterial endocarditis—enterococci, alpha hemolytic streptococci and nonhemo-

lytic streptococci—have usually resisted attack by any one agent given alone. As previously discussed, the increasing incidence of staphylococcal resistance has become a serious problem.[1, 8–10, 15, 16, 24] Other organisms that now show a significant incidence of resistance, or are naturally resistant organisms seen more often in clinical infections, are the coliforms and related gram-negative bacilli.[6, 17, 18, 21, 23]

These four groups—Pseudomonas and Proteus, nongroup A streptococci, staphylococci, and coliform and related species—are the principal bacteria that constitute a clinical problem. The problem in the case of the tubercle bacillus is prevention of resistance rather than treatment. Our discussion, then, will be primarily concerned with those antimicrobials that may form useful combinations in that their synergism offers a solution to some aspect of the therapeutic problems specified.

The Clinically Useful Antimicrobial Agents

The term "resistant" does not denote an *absolute* lack of susceptibility to various available agents—merely failure to be affected by levels that are achieved in the body by usual doses. Actually, the microorganisms with which we are concerned show a susceptibility pattern similar to that of more sensitive related species. Thus we may expect the gram-positive cocci to be affected by certain agents, but to require a higher level than can be achieved clinically. Similarly the gram-negative bacilli follow the general pattern of their more sensitive relatives. This understanding is necessary in order to know what agents warrant considering at all. The agents to be considered in a specific infection will be those that have *some* activity, even though it is not capable of inhibiting the microorganism at levels in the body that can be achieved with usual clinical doses. The aim is to obtain a synergistic effect by the combined action of two agents in usual doses, although such doses of either alone would be ineffective.

The antimicrobial agents that warrant consideration for our purposes have been classified into two groups by Jawetz and co-workers:[12, 14] (I) penicillin, streptomycin, bacitracin, polymyxin B; (II) tetracycline (or oxytetracycline), chloramphenicol, erythromycin (or carbomycin), sulfonamides.

Synergism is encountered most commonly among drugs of group I and occasionally when a drug of group II is combined with an agent of group I, but not among drugs of group II. One need not consider antagonism, inasmuch as this phenomenon is not encountered clinically with any reasonably appropriate combination in the treatment of any of the infections we have listed as appropriate indications for the use of combinations.[12]

Laboratory problems related to the selection of antimicrobial agents, including tests for bacterial sensitivity to combinations, have been discussed by Fink[7] and by Jawetz and co-workers.[14]

Management of Patients

With the increasing need for dealing with infections caused by organisms resistant to any one agent alone, we are naturally desirous of applying available knowledge regarding the synergistic potentialities of antimicrobial combinations. The procedure in the management of a serious infection should be to institute the therapy most likely to prove effective without waiting for laboratory testing of sensitivity. Specimens for laboratory tests should be taken, of course, so that sensitivity data may be obtained as promptly as possible in case the therapy chosen on the basis of clinical criteria should prove ineffective.

While the laboratory tests are being made, therapy of a serious staphylococcal infection may be instituted with a combination of erythromycin and a broad-spectrum antibiotic. Endocarditis caused by alpha hemolytic or nonhemolytic streptococci may be treated with a combination of penicillin and streptomycin. In the same circumstances infections with coliforms may be treated with a combination of streptomycin and a broad-spectrum antibiotic (tetracycline or oxytetracycline), Pseudomonas infections with a combination of oxytetracycline and streptomycin,[2, 3] and Proteus infections with tetracycline (or oxytetracycline) in combination with penicillin and perhaps a sulfonamide.

Milder infections caused by any of the organisms under consideration here should usually be left untreated until sensitivity tests have been made and definitive treatment determined on the basis of their results.

SUMMARY

It seems clear that the problem of antibiotic resistance of bacteria is one largely of replacement of sensitive by resistant bacterial strains during the use of antimicrobial agents, or by cross infections in hospitals where these agents are widely used. Most of the common pathogenic bacteria have retained their sensitivity to most of the useful antibiotics.

In the case of the staphylococcus the prevalence of resistant strains is related to the closeness of association with hospitals where antibiotics are widely used.

Resistance to streptomycin, when used alone, is a problem in all infections, particularly in tuberculosis, but for the most part resistance to this agent is limited to the patients who are treated and can be combated by the conjoint use of a second agent also active against the

specific organism. The application of this principle of combined therapy to the type of resistance exemplified by the staphylococcus warrants investigation.

The bacterial species that are most often clinical problems because of their natural resistance to all available antimicrobial agents or because the intensive use of these agents has permitted formerly rare resistant mutants to proliferate and change the character of the species to one composed of frequently resistant strains are staphylococci, enterococci and nonhemolytic streptococci, Pseudomonas and Proteus, and gram-negative bacilli of the coliform group. The use of combinations of appropriate antimicrobial agents for their synergistic action, although they lack effectiveness when used singly, offers the best solution to these clinical problems at present.

REFERENCES

1. Barber, M., and Burston, J.: Antibiotic-Resistant Staphylococcal Infection. *Lancet*, 2:578, 1955.
2. Carroll, G.: The Changing Flora in Urinary Infections in This Antibiotic Age. *J. Urol.*, 73:609, 1955.
3. Carroll, G., Brennan, R. V., and Allen, H. N.: Combined Therapy with Oxytetracycline and Streptomycin in the Treatment of Urinary Tract Infections Caused by *Pseudomonas* Organisms. *Antibiotics Ann.*, 2:959, 1954–55.
4. Dowling, H. F., Lepper, M. H., and Jackson, G. G.: When Should Antibiotics Be Used in Combination? *J.A.M.A.*, 151:813, 1953.
5. Dowling, H. F., Lepper, M. H., and Jackson, G. G.: Clinical Significance of Antibiotic-Resistant Bacteria. *J.A.M.A.*, 157:327, 1955.
6. Etteldorf, J. N.: Diarrhea in Infancy. *M. Times*, 83:1137, 1955.
7. Fink, F. C.: Laboratory Problems Related to Antibiotics and Chemotherapy. *Pub. Health Lab.*, 11:44, 1953.
8. Finland, M.: Clinical Uses of Presently Available Antibiotics. *Antibiotics Ann.*, 1:10, 1953–54.
9. Finland, M.: Changing Patterns of Resistance of Certain Common Pathogens to Antimicrobial Agents. *New England J. Med.*, 252:570, 1955.
10. Finland, M.: Antibiotic-Resistant Micrococcic Infections. *J.A.M.A.*, 158:188, 1955.
11. Hobby, G. L., Lenert, T. F., and Pikula, D.: Antimicrobial Agents—Their Activities Alone and in Combination. *Antibiotics Ann.*, 1:294, 1953–54.
12. Jawetz, E.: Combined Antibiotic Action—Experimental and Clinical. *Antibiotics Ann.*, 1:41, 1953–54.
13. Jawetz, E.: The Forgotten Host. *Stanford M. Bull.*, 13:84, 1955.
14. Jawetz, E., Gunnison, J. B., Coleman, V. R., and Kempe, H. C.: A Laboratory Test for Bacterial Sensitivity to Combinations of Antibiotics. *Am. J. Clin. Path.*, 25:1016, 1955.
15. Knight, V., and Collins, H. S.: A Current View of the Problem of Drug-Resistant Staphylococci and Staphylococcal Infection. *Bull. New York Acad. Med.*, 31:549, 1955.
16. Lepper, M. H.: Microbial Resistance to Antibiotics. *Ann. Int. Med.*, 43:299, 1955.
17. Limson, B. M., Shea, J. G., and Romansky, M. J.: Acute and Chronic Pulmonary Infection with the Friedländer Bacillus. *Antibiotics Ann.*, 3:786, 1955–56.
18. Lind, H. E., and Swanton, E. M.: Chemotherapy of Urinary Infections. *Antibiotics Ann.*, 3:778, 1955–56.

19. Lowbury, E. J. L.: Cross-Infection of Wounds with Antibiotic-Resistant Organisms. *Brit. M. J.*, 1:986, 1955.
20. Monnier, J., and Quercy, J.: La résistance bactérienne croisée aux antibiotiques. *Cong. franç. méd.*, 30:201, 1955.
21. Spink, W. W.: Present Therapy of Brucellosis. *Antibiotic Med.*, 1:250, 1955.
22. Szybalsky, W.: Genetic Studies on Microbial Cross-Resistance to Toxic Agents. *Antibiotics & Chemother.*, 3:1095, 1953.
23. Turell, R., Vallecillo, L. A., Paradny, R., and Danza, A. L.: Preoperative Preparation of the Colon with Sulfonamides or Antibiotics. *S. Clin. North America*, 35:1, 1955.
24. Wright, S. S., Purcell, E. M., Wilcox, C., Broderick, M. K., and Finland, M.: Antibiotic Combinations and Resistance to Antibiotics. *J. Lab. & Clin. Med.*, 42:877, 1953.
25. Wright, W. A., Boyer, D. D., and Strode, J. W.: Genetic Aspects of Antimicrobial Therapy. *Antibiotics Ann.*, 3:27, 1955–56.

630 Flushing Avenue
Brooklyn 6, New York

DIAGNOSIS AND ANTIMICROBIAL THERAPY IN INFECTIONS OF THE RESPIRATORY TRACT

JOHN M. ADAMS, M.D.

WILLIAM L. HEWITT, M.D.

Before any discussion of the use of antimicrobial therapy in the various respiratory tract infections in children, consideration of the diagnosis of these diseases is almost obligatory.

DIAGNOSIS

Consideration of diagnosis involves some agreement and understanding of the terminology or classification of respiratory diseases. Such terms as tonsillitis, nasopharyngitis, bronchitis or "the virus" are of little value and are almost meaningless when it comes to making a decision as to the proper or best therapy for the patient. We realize that when we depreciate these general terms, we must offer something better. This is not an easy assignment, but as physicians we can begin to acquire an etiologic viewpoint about these diseases and come closer to an accurate diagnosis which will permit a more intelligent approach to the treatment of our patients.

Although an attempt will be made to outline the acute respiratory tract infections in order that we may arrive at a better understanding of them, in no sense is this outline meant to represent a classification of all these diseases. It will help, however, to have some common terminology and grouping of these illnesses. The diagnostic features of several of them will be discussed separately or as a group in the first part of this clinic, and a discussion of the treatment of many of them will follow in the second part. The practical diagnosis of these often

TABLE 10. *Acute Respiratory Tract Infections*

DISEASES	TYPE	ETIOLOGY
Epidemic influenza	Influenza A Influenza B Influenza C	Influenza A virus Influenza B virus Influenza C virus
Common colds or acute respiratory disease	Coryza type (afebrile) APC* (febrile)	Undetermined APC & RI 67 group
Exudative tonsillitis and/or pharyngitis	Streptococcal type Nonstreptococcal type	Beta hemolytic streptococcus APC & RI 67 group
Vesicular pharyngitis	Herpangina	Coxsackie A viruses
Scarlet fever	With rash Without rash	Beta hemolytic streptococcus Erythrogenic toxin-producing Beta hemolytic streptococcus
Measles	Rubeola Rubella	Rubeola virus Rubella virus
Lymphocytic choriomeningitis	Respiratory type	Lymphocytic choriomeningitis virus
Infectious mononucleosis	Pharyngeal type	Undetermined
Q fever	Rickettsial disease	Coxiella burnetii
Ornithosis	Psittacosis, etc.	Psittacosis-ornithosis group of viruses
Tuberculosis	Pulmonary	Tubercle bacillus
Moniliasis		Candida albicans
Histoplasmosis		Histoplasma capsulatum
Coccidioidomycosis		Coccidioides immitis

* Adenoidal-pharyngeal-conjunctival.

vague and ill defined diseases still must depend largely on clinical methods, such as a good history and physical examination. An appreciation of the newer advances in our knowledge of them is also essential to better and more meaningful diagnoses.

Influenza

Fortunately, some significant and important strides have been made in our knowledge of etiology of some of the common respiratory tract infections.

Three immunologically distinct types of influenza are now recognized, and these can be diagnosed accurately today, not only in research and service laboratories, but in many city, state and national public health laboratories. The influenzas are cyclic epidemic diseases which most commonly occur in the winter months. In infants and children the onset is abrupt, high fever, lassitude and signs of toxicity being the most striking symptoms and signs.[1] These are all features which are important in making this clinical diagnosis. A diagnosis of influenza outside of an epidemic period is almost bound to be incorrect, whereas during an epidemic the majority of acute respiratory tract infections are probably due to one of the influenza viruses.

Common Colds and Adenoidal-Pharyngeal-Conjunctival (APC) Viruses

The undifferentiated respiratory diseases, including the febrile acute respiratory diseases, exudative nonstreptococcal pharyngitis and primary atypical pneumonia, as well as the afebrile common colds, continue as unsolved omnipresent sources of human disease. By means of suitable tissue culture systems several newly recognized viruses have been revealed as causes of undifferentiated respiratory tract infections. The investigators at the Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, headed by Dr. Robert J. Huebner, have been successful in isolating from tonsils and adenoid tissues several strains of immunologically distinct viruses which produce disease in man.[10, 20] They have proposed the term adenoidal-pharyngeal-conjunctival (APC) agents as the generic designation of this new group of viruses.

New agents have also been reported by Hilleman and Werner[8] in patients with acute respiratory illnesses, and by Neva and Enders[17] in a patient with an illness resembling roseola infantum. They have successfully isolated an agent which has been classified as type 3 in this new group of APC agents. A type 1 strain was recovered from pharyngeal secretions of a two year old infant taken on the first day of an acute febrile illness with exudative pharyngitis. Type 5 was demonstrated in a laboratory technician suffering from an acute sore throat and earache without apparent fever. However, the types 3 and 4 have been recovered almost exclusively from persons with some type of respiratory disease. The type 3 agent was isolated in an epidemic in northern Virginia in the throat, conjunctival and anal excretions of 76 patients. At the same time similar isolation attempts in 85 controls who were not ill were negative. Although conjunctivitis was a striking feature of this epidemic and associated with swimming pool contacts, no evidence of inclusion conjunctivitis was found. A type 4 virus (named RI 67 by Hilleman and Werner) was encountered seven times

in the nasopharyngeal secretions of patients studied with acute respiratory illnesses. Their illnesses were characterized by fever, sore throat and nasal congestion, accompanied by discharge and cough. Tonsillitis, pharyngitis, hoarseness and coryza were the prominent symptoms and signs.

Although the tissue culture methods have revealed some 10 to 11 types,[3] not all of these have yet been established as producing acute respiratory disease. However, from serologic evidence nearly all these types produce infections in man. The type 1 and 2 agents, for example, appear to be extremely common, occurring most frequently in the first few years of life. The most important properties to be considered in the definition of the entire group are as follows: complement-fixing antigen common to the group, characteristic cytopathogenic effects in human epithelium and in HeLa cells, a pathogenicity for common laboratory animals and ether resistance. It is important to point out that they are also resistant to the sulfonamide drugs and all antibiotics to which they have been subjected to date. According to Huebner, all of the first six types cause frequent infections in man beginning at an early age, based on serologic surveys which indicate that 50 per cent of infants six months to one year of age have been infected with at least one type.

RI 67 Group

Infection with viruses of the RI 67 group accounts for a large portion of the respiratory illnesses designated as undifferentiated acute respiratory disease (ARD) and primary atypical pneumonia in which the cold agglutinins are negative. This is well established, particularly among new recruits in army populations undergoing basic training. Epidemics may occur with influenza, but also will occur in the warm summer months when influenza is uncommon. Patients with infection due to RI 67 may be ill enough to require hospitalization in about 25 per cent when seen in camp epidemics; another 25 per cent will seek treatment in the dispensary; while the remainder will have illnesses which are extremely mild or inapparent. The most severely ill complain of sore throat, nasal congestion and cough and show signs of tonsillitis and pharyngitis, often with the characteristic whitish pinpoint exudate on the tonsils or pharynx.

Coxsackie or C Viruses

Within the last few years the Coxsackie or C viruses have been recognized commonly, and in at least one respiratory disease, vesicular pharyngitis, some of the group A Coxsackie viruses have been shown to be etiologic factors. This disease, which has also been designated as

herpangina, is characterized by vesicles on the pharyngeal wall which later ulcerate and finally heal in seven or eight days. The initial illness is limited to a febrile period of about 48 hours and is commonest in the summer months in children. These clinical features may be helpful in differentiating this disease from poliomyelitis and other summer illnesses.

Lymphocytic Choriomeningitis

Some explanation is required when a disease that is commonly considered to involve the central nervous system is included in a paper on acute respiratory tract infections. This virus is capable of producing acute respiratory disease in man with symptoms and signs similar to those of influenza. Early in the history of lymphocytic choriomeningitis a grippelike illness was recognized as developing among laboratory workers. Serums from 1248 persons were tested by Armstrong and Wooley,[2] and 138, or 11 per cent, were found to contain protective antibodies against the virus. Histories revealed upper respiratory symptoms as the only ones common to the groups tested. One hundred and six serums from persons with recent upper respiratory infection showed positive tests in 28.3 per cent. The virus of choriomeningitis occurs naturally in several animals, including mice, guinea pigs, monkeys and dogs. The disease assumes an important public health role, because the causative agent is present in certain lower animals commensal with man, such as the gray or house mouse (*Mus musculus*), which eliminates virus from its nasal secretions, semen, urine and feces. Further study of the clinical features, particularly of the mild respiratory illnesses probably caused by this virus, are greatly needed.

Infectious Mononucleosis

Studies of infectious mononucleosis have shown that its clinical features frequently involve the respiratory passages. As high as 80 per cent of patients with this disease were found to have tonsillitis and/or pharyngitis and an increased incidence of atypical pneumonia.[11] The etiologic factor in infectious mononucleosis is not yet known, but this disease has been assumed to be due to a virus. Diagnostically, careful studies of the blood which reveal a lymphocytosis with some abnormal cells may be most helpful in making an accurate diagnosis. A positive heterophile agglutination test is also of diagnostic import.

Rickettsial Diseases

Certain rickettsial diseases, the most striking of which is Q fever, may produce respiratory tract infection characterized often by an atypi-

cal form of pneumonia. No practical tests for an accurate early diagnosis of Q fever are available, but the history of contact with dairies or meat packing plants and the physical findings in these patients may lead to this diagnosis. Complement-fixation tests are available and may be most valuable in confirming this disease.

Ornithosis

Further causes of primary respiratory disease include the ornithosis viruses, which are carried and spread by many different types of birds, including the common barnyard fowl, as recently demonstrated by Dr. K. F. Myer. Contact with parrots, parakeets, pigeons and other birds should suggest the possibility of a diagnosis of ornithosis. When this diagnosis is made, the appropriate antibiotic may wisely be administered.

Tuberculosis, Coccidioidomycosis, Histoplasmosis

The importance of the tuberculin test cannot be overemphasized as a tool for the accurate diagnosis of tuberculosis. In children, in particular, it is important to perform and record previous negative tests in a good preventive or well baby care program. When exposure is known and a positive test is revealed, early detection is possible by means of the tuberculin test. Confirming diagnostic procedures, however, must depend on the isolation of the tubercle bacillus. By direct smear and cultural methods this organism may be accurately isolated and thus diagnosis established.

Hypersensitivity of the skin has been found to be most helpful in the diagnosis of coccidioidomycosis and histoplasmosis, and both these diseases may be regarded as respiratory tract infections. The history of living in an endemic area may be most important as an aid to diagnosis of these diseases.

Miscellaneous Respiratory Diseases

Certain miscellaneous and relatively infrequent causes of respiratory tract involvement must be kept in mind in attempting to arrive at an etiologic diagnosis of these diseases. Chemical causes, such as the aspiration of kerosene, are well known to most physicians who care for small children. Beryllium may be a cause of pneumonitis, and many other agents such as dusts and powders which are aspirated into the lung may serve as etiologic factors of disease. Other forms of pulmonary disease, such as eosinophilic pneumonia or allergic pneumonia, may in rare

instances be the correct diagnosis. The pulmonary tract may be involved in connection with acute rheumatic fever, and this disease often defies accurate diagnosis, but the value of a good history and physical examination may be paramount in suggesting the correct diagnosis.

A complete categorization of the causes of acute respiratory disease is not possible, but this brief survey may serve to point out that if we use all the clinical and laboratory tools at our disposal and are aware of the tremendously varied etiologic agents which may be involved in producing disease in the pulmonary tree, we shall have a means by which we can arrive competently at more accurate diagnoses.

The Clinical Spectrum and Age Factors

We have attempted to point out the extreme importance of an etiologic approach to the respiratory tract infections in order that a wise choice of antimicrobial therapy may be made for our patients. The second concept which is vital to our understanding of these diseases is that basically they manifest themselves in a wide variety of symptoms and signs from inapparent disease through mild, moderate and severe illness, even to death. This clinical gradation may reveal itself in single family epidemics, but is more apparent in community epidemics when we are aware of the widespread clinical features of most of these diseases.

Age factors would appear to play a significant role in the clinical spectrum of disease. Some infections are much more severe in prematurely born babies than they are in older individuals and adults. The contrary can also be true, since we know that infants may have poliomyelitis with minor paralysis, whereas older individuals and adults may have the more severe forms of this disease. Experimentally, factors of age are significant in certain infectious diseases; for example, suckling and newborn animals may be quite susceptible to certain types of infection such as Coxsackie viruses, whereas older animals are much more resistant.

Primary and Secondary Disease

It seems important to be fully aware of what infectious agents are capable of causing primary disease and what agents are most likely to cause secondary complications. There are undoubtedly many primary infectious agents, probably for the most part in the category of viruses. Organisms of a bacterial or fungal nature which are capable of producing disease, particularly as secondary or complicating factors, are also numerous, and it is possible to visualize almost innumerable combina-

tions of infection which may vary from epidemic to epidemic and community to community. The various influenza viral infections and measles have been recognized for many years as primary infections which may be commonly complicated by secondary bacterial infection.

Croup and laryngitis are undoubtedly not related to any single specific infectious agent, but are forms of respiratory disease in which several rather distinct clinical patterns must be differentiated one from the other. It seems logical to assume that any of the primary respiratory agents in the proper host might produce the symptom picture of croup. However, we recognize that such well known viral agents as influenza A, B and C, rubeola and C viruses do not usually cause croup or laryngitis per se. Simple croup, often referred to as spasmodic or false croup, is nearly always associated with a mild respiratory tract infection and may include many of those outlined briefly in the preceding pages. The condition is self-limited and is characterized by rather sudden onset of spasm of the larynx in the middle of the night, which responds quickly to treatment. There are evident predisposition and familial tendencies in the children affected by this condition.

On the other hand, acute laryngitis, which is usually a secondary complication, is characterized by a temperature elevation, greater toxicity and failure to respond to treatment as promptly as simple croup. Diphtheritic laryngitis is slower in onset, the temperature is lower, and the toxicity is usually greater than in the nondiphtheritic form. Acute infective laryngeal tracheobronchitis is characterized by acute inflammation of the larynx, trachea and bronchi and marked subglottic edema with nonmembranous exudate. Secondary complicating bacterial organisms are considered to be etiologically important in producing these complications of primary respiratory disease characterized in some patients by croupy symptoms. The wise selection of the proper antimicrobial agent has been shown to be lifesaving in this serious disease of infancy. Prior to the advent of antimicrobial therapy the mortality in this disease was very high, indeed.

The etiologic agent, whether it be primary or secondary, should be sought by all the means at our disposal, keeping in mind the great importance of a good history and physical examination. Cultural methods for the isolation of many of the viral, bacterial and fungal agents, as well as complement-fixation and immunologic procedures, are available in many laboratories. The importance and the frequency of mixed infections have been alluded to, but should not deter us in attempting to get at one or another of the causative agents. In severe forms of acute respiratory disease and particularly in the complications, cultures of the blood and various other secretions or exudates, such as from the middle ear, should be made whenever possible. If meningitis is suspected, it is wise and important to withhold specific therapy until

a spinal puncture has been accomplished. Appropriate specific therapy can usually be found if the exciting agent is properly diagnosed.

It has been rather widely assumed that the use of antimicrobial agents was advisable in many patients for the prevention of secondary complications, particularly the bacterial ones which may occur commonly in concert with many of the primary respiratory tract infections. Recent studies by Weinstein[23] have given some real reasons to reconsider this problem, for he has shown that in a great many patients with measles, antimicrobial therapy not only is ineffective in preventing bacterial complications, but also may increase the risk of their development. As pointed out in an editorial on this subject in *The New England Journal of Medicine* (Oct. 20, 1955), there is a need for critical review of routine prophylactic use of antibiotics in simple nonbacterial infections, many of which have been discussed in this clinic.

TREATMENT

Rickettsial Diseases

Chloramphenicol, tetracycline and its derivatives continue to be the best agents and about equally so for treatment of all the rickettsial diseases.[16, 21] The same schedule may be used for any of these diseases and consists of an initial oral loading dose of 50 mg. per kilogram of body weight followed by a daily dose of 50 mg. per kilogram divided into doses at six hour intervals. This should be continued until the patient has been afebrile for two to three days. Two to four days of treatment are required to abolish fever and constitutional symptoms. The time required to establish a clinical response seems to be characteristic for different rickettsial infections, but only rarely should more than five days be required.

The possibility of relapse is important in certain of the rickettsial diseases, particularly if treatment is instituted late in the course of the disease. Recrudescence of disease occurs five to seven days after antibiotic therapy has been discontinued. The incidence of relapse decreases progressively with the duration of illness prior to treatment. If treatment is begun during the first week of illness, relapses may be prevented by administering a 50-mg. per kilogram supplementary dose of antibiotic about the fourth day after completion of the initial course of treatment.

Ornithosis

Penicillin in high dosage has been reported to have some value in this disease. Chloramphenicol and the tetracyclines are effective in experi-

mental infections, and scattered clinical evidence indicates that they are effective in human infections.[6, 18] They are the agents of choice and should be administered in a fashion similar to that indicated for the rickettsial diseases.

Viral Respiratory Diseases

These diseases, which must be discussed separately from the standpoint of etiology, can be considered together for therapeutic considerations, since presently available chemotherapeutic agents do not influence the course of the viral disease per se. With the exception of primary atypical pneumonia (PAP), this fact is relatively widely appreciated. Primary atypical pneumonia is probably caused by a number of agents, including those producing the rise in cold agglutinins and Streptococcus MG agglutinins, the group designated RI 67, and probably a considerable number of other viruses. Much less enthusiasm now exists regarding the effectiveness of broad-spectrum antibiotic agents in this group of pneumonias. Recent controlled studies have indicated that these agents have little if any effect on the course of the disease.[22] In seriously ill patients, however, a brief trial of the tetracycline drugs may be worth while.

Prophylactic administration of antibiotic agents or sulfonamides for suppression of bacterial complications of viral respiratory diseases is a frequent consideration and subject to considerable disagreement. Since the introduction of sulfonamides and antibiotic agents they have seen used for prevention of bacterial complications of viral diseases. Variable success has been noted, some authors reporting almost complete elimination of secondary pyogenic infection[4, 9, 13, 14] and others presenting good evidence precisely to the contrary.[5, 7, 12, 23] A recent carefully controlled study[23] indicated that the incidence of pyogenic infections of the upper and lower respiratory tracts complicating viral infections such as measles is not decreased by the administration of antibiotic agents and, indeed, may even be increased. Sensitive bacteria in the respiratory tract are replaced by resistant organisms upon administration of therapeutic doses of antimicrobial agents or after smaller prophylactic doses of these agents with the exception of the very small doses of penicillin necessary for prophylaxis of beta hemolytic streptococcal infections. Particularly after administration of the tetracyclines, increased numbers of Proteus, Pseudomonas, *Staphylococcus aureus and Candida albicans* appear. The secondary pyogenic infections which occur in the wake of antibiotic prophylaxis are commonly due to these resistant bacteria rather than the usual pneumococci or beta hemolytic streptococci. It is probably wise, therefore, to observe

carefully for the appearance of suppurative complications and treat them when they arise.

Bacterial Infections

Pneumonias. Specific therapy of bacterial pneumonia should be based upon laboratory diagnosis of the etiologic agent and should not be reserved for those cases failing to respond. All cases of moderately severe or severe pneumonia should have at least a gram-stained smear and culture of the sputum and preferably also a blood culture before starting therapy. It is obviously impossible in most situations to await the results of these studies before starting treatment. If the pulmonary infection is severe, penicillin and streptomycin or penicillin and tetracycline should be administered at once. If the infection is mild or moderately severe, tetracycline should be an adequate drug for the vast majority of cases. Twenty-four hours later preliminary laboratory results will be available to make a more specific decision in the treatment of the severe pneumonias.

Penicillin or tetracycline is the treatment of choice for pneumococcal or streptococcal pneumonias. No differences have been observed in the response to these two agents, although the relative incidence of complications following their use is not known. If the clinical disease is mild or moderately severe without complications, or if the infection is almost certainly due to one of these very sensitive bacteria, oral penicillin may be given. Recent evidence indicates that, pharmacologically, oral penicillin V is somewhat superior to penicillin G. The comparative therapeutic efficacy is not firmly established. Marked improvement frequently occurs in 24 hours and almost always in 48 hours. The duration of treatment should be for three to four days of essentially normal temperature. Failure to respond promptly should suggest a mistake in diagnosis such as a nonbacterial infection or infection due to Friedländer's bacillus, *Hemophilus influenzae, Staphylococcus aureus* or tuberculosis or lung abscess. A suppurative complication such as empyema, meningitis, endocarditis or arthritis may also exist. Fluid from serous cavities may be sterile if antibiotic therapy has been previously administered; if so, penicillin need not be administered into the serous cavity.

Pulmonary Infections. The importance of antibiotic-resistant staphylococci as a cause of suppurative pulmonary infections is progressively increasing. These infections should be suspected and treated early and intensively because of the rapid formation of necrotic foci which are then inaccessible to antibiotic agents. If penicillin-resistant organisms are the etiologic agents, the use of a combination of agents is important

for the increased therapeutic efficacy which may be obtained and possibly to delay the emergence of further antibiotic resistance, although no clear evidence is available to substantiate the latter. Particularly if a patient has been previously treated with antibiotic agents or if he has been exposed to a hospital environment where these resistant organisms are prevalent, the antibiotic sensitivity of these bacteria should be determined at once. If the organism is penicillin-sensitive, and until it is shown not to be, crystalline potassium penicillin G is the agent of choice and should be administered in high dosage. If the staphylococcus is penicillin-resistant or if the patient falls into either of the two categories mentioned, the organism may be sensitive to tetracycline, but is almost certain to be sensitive to chloramphenicol. Because of the seriousness of this problem, maximal doses of chloramphenicol and erythromycin should be given from the onset with the judicious addition of bacitracin if renal function is normal.

Response of staphylococcal infection is slower than in the case of pneumococcal or streptococcal infections, but failure to respond in four or five days requires complete re-evaluation of antibiotic sensitivity and a careful search for necrotic foci which are inaccessible to chemotherapy, but might be available for drainage. Because of the longer periods for healing such foci, chemotherapy should be continued for two to three weeks after the temperature is normal and all clinical and roentgenologic evidence of disease is resolved.

Two new antibiotic agents, Albamycin (Upjohn) and Cathomycin (Merck & Co.), are currently in the investigational stage and bear some promise for the management of resistant staphylococcal infections. They show no cross resistance with penicillin, tetracycline or erythromycin, are well absorbed when administered orally, produce high serum levels, do not possess significant toxicity to the extent to which observations have currently progressed, and have produced suggestively favorable therapeutic results in a limited number of cases.

Acute pulmonary infections due to Friedländer's bacillus are infrequent but important because they do not respond to penicillin and are rapidly progressive, the deaths usually occurring in those cases which have not received sufficient treatment. Chronic cases with abscesses or cavities usually arise from acute cases neglected for 48 hours or longer. The antibiotic sensitivity of these bacteria varies considerably and sensitivity tests in vitro are indicated. Streptomycin combined with tetracycline or chloramphenicol is the treatment of choice. Streptomycin should be continued for several days after the temperature has become normal and tetracycline for two weeks of normal temperature. Sulfadiazine is undoubtedly of value in some cases and should be administered in combination with one or more of the foregoing antibiotics.

Infections due to *Hemophilus influenzae* are best treated with tetracycline. Streptomycin is also effective. Laryngeal or tracheal obstruction due to epiglottitis may be prevented by prompt recognition and treatment of infections due to this organism.

Primary tuberculosis in infancy, particularly when it is detected early in its development, should be considered for specific treatment by isoniazid (INH) (4 to 5 mg. per kilogram of body weight). Lincoln[15] suggests that this therapy might prevent the serious complication of tuberculous meningitis. Robinson et al.[19] treated four infants effectively, and all the patients had a reversion in the tuberculin reaction. Any infant under one year of age who is found to have a positive Mantoux test is considered an early converter and therefore a candidate for treatment. Active tuberculosis should be treated with at least two of the antimicrobial agents (INH, streptomycin, para-aminosalicylic acid).

The treatment of histoplasmosis and disseminated coccidiodomycosis remains unsatisfactory. Some alteration in the course of histoplasmosis seems to have followed administration of ethyl vanillate and dihydroxystilbamidine. The same is true for disseminated coccidioidomycosis. Nystatin has had a beneficial effect in the latter disease when administered parenterally, but is not absorbed from the gastrointestinal tract. The intravenous preparation of nystatin is, unfortunately, relatively insoluble and extremely irritating locally.

SUMMARY

The respiratory tract infections have been reviewed from the viewpoint of diagnosis and treatment, with emphasis given to the importance of the etiology of disease as a means of determining the best therapy for the patient. The diseases have been outlined and terminology suggested which is in keeping with causative factors.

The clinical spectrum extending from inapparent disease to death in most of these diseases is discussed briefly with a consideration of the importance of age as a factor in the severity of the clinical manifestations. Primary and secondary disease must be given consideration with the realization that primary infections may frequently be complicated by secondary causative factors and mixed infections of various types may result.

The drugs of choice for therapy of rickettsial infections and those due to the ornithosis group of viruses are the tetracyclines. The course of other viral infections per se is not significantly altered by antibiotic agents. The value of prophylactic administration of antibiotic agents to prevent secondary bacterial infection in viral diseases is extremely dubious. This practice may result in no decrease in bacterial complica-

tions, and when infections occur, they may be due to antibiotic-resistant bacteria.

The agents of choice for various specific bacterial infections have been outlined.

REFERENCES

1. Adams, J. M., Thigpen, M. P., and Rickard, E. R.: An Epidemic of Influenza A in Infants and Children. *J.A.M.A.*, 125:473, 1944.
2. Armstrong, C., and Wooley, J. G.: Benign Lymphocytic Choriomeningitis; Laboratory Studies with Virus and Their Possible Bearing on Infection in Man. *J.A.M.A.*, 109:410, 1937.
3. Bell, J. A.: New Vaccine Helps Prevent Colds. *U.S. News & World Report*, Nov., 1955, p. 38.
4. Coburn, A. F.: Prevention of Respiratory Tract Bacterial Infections by Sulfadiazine Prophylaxis in United States Navy. *J.A.M.A.*, 126:88, 1944.
5. Cronk, G. A., Naumann, D. E., McDermott, K., Menter, P., and Swift, M. B.: Uncontrolled Study of the Effect of Oral Penicillin G in the Treatment of Nonspecific Upper Respiratory Infections. *Am. J. Med.*, 16:804, 1954.
6. French, E. L., Joske, R. A., Bodycomb, D. H., McKenzie, E. F., and Rigg, C. R.: Psittacosis in Australia. *M.J. Australia*, 41:392, 1954.
7. Gibel, H., and Litvak, A. M.: Sulfathiazole in the Treatment of Measles and Its Complications. *J. Pediat.*, 21:315, 1942.
8. Hilleman, M. R., and Werner, J. H.: Recovery of New Agent from Patients with Acute Respiratory Illness. *Proc. Soc. Exper. Biol. & Med.*, 85:183, 1954.
9. Holbrook, W. P.: Army Airforces Rheumatic Fever Control Program. *J.A.M.A.*, 126:84, 1944.
10. Huebner, R. J., Rowe, W. O., Ward, T. G., Parrott, R. H., and Bell, J. A.: Adenoidal-Pharyngeal-Conjunctival Agents. *New England J. Med.*, 251:1077, 1954.
11. Hoagland, R. J.: Infectious Mononucleosis. *Am. J. Med.*, 13:158, 1952.
12. Jones, P. N., Bigham, R. S., Jr., and Manning, P. R.: Use of Antibiotics in Nonbacterial Respiratory Infections. *J.A.M.A.*, 1953:262, 1953.
13. Karelitz, S., King, H., Curtis, B., and Wechsel, M.: Use of Aureomycin and Penicillin in Treatment of Rubeola in Pre-eruptive and Early Eruptive Phase. *Pediatrics*, 7:193, 1951.
14. Karelitz, S., Chang, C. C., and Mathews, Z. E.: Prophylaxis and Treatment of Bacterial Complications of Measles with Benzethacil and Aqueous Procaine Penicillin G. *J. Pediat.*, 44:357, 1954.
15. Lincoln, E. M.: Tuberculosis in Children. *Nat. Tuberculosis Bull.*, 40:43, 1954.
16. Liu, R. S. J., Adams, C. B., Jr., Schneider, M. J., Gauld, J., and Parker, R. T.: Clinical Observations with Tetracycline in Certain Rickettsial and Bacterial Infections, in *Antibiotic Annual 1954–55*. New York, Medical Encyclopedia, Inc., 1955, p. 556.
17. Neva, F. A., and Enders, J. F.: Isolation of Cytopathogenic Agent from Infant with Disease in Certain Respects Resembling Roseola Infantum. *J. Immunol.*, 72:315, 1954.
18. Perlman, L., and Milzer, A.: Psittacosis, a Report of Seven Cases. *A.M.A. Arch. Int. Med.*, 94:82, 1954.
19. Robinson, A., Meyer, M., and Middlebrook, M.: Tuberculin Hypersensitivity in Tuberculous Infants Treated with Isoniazid. *New England J. Med.*, 252:983, 1955.
20. Rowe, W. P., Huebner, R. J., Gilmore, L. K., Parrott, R. H., and Ward, T. G.: Isolating of a Cytopathogenic Agent from Human Adenoids Undergoing Spontaneous Degeneration in Tissue Culture. *Proc. Soc. Biol. & Med.*, 84:570, 1953.

21. Smadell, J. E.: Antibiotic Therapy of Viral and Rickettsial Diseases. *New York Acad. Med. Bull.*, 31:704, 1955.
22. Walker, S. H.: Ineffectiveness of Aureomycin in Primary Atypical Pneumonia. A Controlled Study of 212 Cases. *Am. J. Med.*, 15:593, 1953.
23. Weinstein, L.: Failure of Chemotherapy to Prevent Bacterial Complications of Measles. *New England J. Med.*, 253:679, 1955.

Additional References

Adams, J. M.: Introductions to Infections of the Respiratory Tract. *Brennemann's Practice of Pediatrics*, 1955, Vol. II, Chap. 39.
Adams, J. M.: Psittacosis. *Brennemann's Practice of Pediatrics*, 1955, Vol. II, Chap. 16.
Barton, W. J., Heilman, F. R., Nichols, D. R., Wellman, W. E., and Gerachi, J. E.: Streptonivicin (Albamycin); A New Antibiotic. *Proc. Staff Meet., Mayo Clin.*, 30:540, 1955.
Editorial: Oral Administration of Penicillin. *New England J. Med.*, 253:789, 1955.
Hewitt, W. L., and Finegold, S. M.: Unpublished data.
Jones, W. F., and Finland, M.: Blood Levels from Orally Administered Penicillins G and V. *New England J. Med.*, 253:754, 1955.

University of California Medical Center
Los Angeles 24, California

ANTIMICROBIAL THERAPY IN GENITOURINARY TRACT INFECTIONS

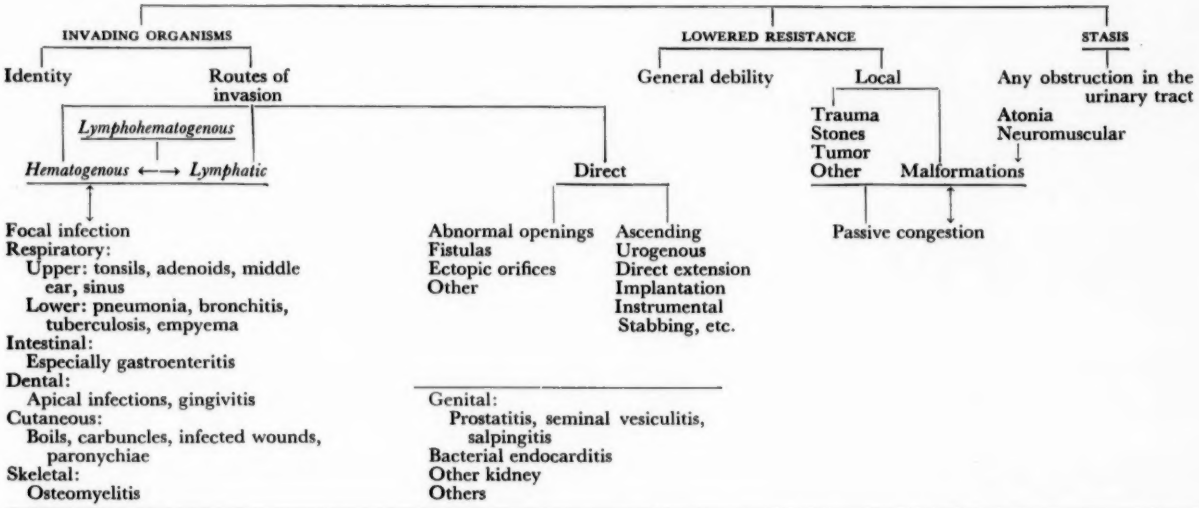
MEREDITH F. CAMPBELL, M.D.

The successful treatment of urinary tract infections requires deeper thinking and greater activity than mere prescription writing. The discovery of the several antibiotics has been a tremendous boon in combating these infections and has saved many lives. The frequent complicating side effects of these antimicrobials, however, have also engendered many new and unforeseen therapeutic and clinical problems and conditions which unintentionally jeopardize the patient (e.g., ulcerative enteritis, exfoliative dermatitis, aplastic anemia). Furthermore, the eradication of these complications has often been more difficult and uncertain than that of the original disease! Recognition of these facts is an essential part of the management responsibility.

ETIOLOGIC CONSIDERATIONS IN URINARY INFECTION

No discussion of treatment of urinary infection can overlook sharp consideration of the more important associated (nonbacterial) causes of the disease. Here urinary stasis (faulty urinary drainage, urinary constipation), usually due to obstruction or neuromuscular dysfunction, ranks first and not only predisposes to the occurrence of urinary infection, but also perpetuates an established one. Sterilization of the urine by feeble antiseptics such as methenamine and even mandelic acid compounds bespeaks absence of important urinary stasis. But with present-day antimicrobial therapy, especially the antibiotics, the urine is sometimes sterilized even though easily demonstrable and often pronounced urinary stasis exists. It must be realized that persistence of

TABLE 11. *Etiologic Factors in Urinary Infections**



*Modified after Vose.

the infection despite intensive properly indicated antibiotic therapy is as frequently due to undiagnosed or disregarded urinary stasis as to bacterial resistance.

The usual predisposing or associated etiologic factors in the development of urinary infection are shown in Table 11. Limitations of space prohibit further discussion of these now; suffice it to note that they require eradication if administration of the new medications is to be most effective. Too often the antibiotic is blamed for therapeutic failure when it really had no chance because of urinary stasis, obstruction, complicating stone, tumor, or the like. Antibiotic therapy is a biologic phenomenon and does not react with chemical precision; that is, if a sensitivity test shows the invading organism(s) sensitive to X antibiotic, the administration of X when stasis or other complicating conditions exist may well fail to sterilize the urine.

SYMPTOMS

The clinical picture in acute urinary infection may be that of "grippe" with fever, perhaps even with chills, generalized aches and malaise with frequency or other alteration of urination and localizing pain along the urinary tract, especially in the kidney region. Gastrointestinal disturbances are variable, but are usually present with nausea, sometimes vomiting, abdominal discomfort, diarrhea, constipation or gaseous distention. On the other hand, in half the cases of acute urinary infection there are no localizing symptoms. In either event, as in the study of any sick patient, *examine the urine!*

Chronic urinary infection may develop insidiously, succeed an uncured acute infection, or may be an accidental discovery. Chronic pyuria with urinary and intestinal disturbances are the usual symptoms, but there may be none except pus in the urine. Pain usually reflects urinary distention, especially in the bladder, ureter or kidney, and may be mild or severe. Upon identification of the invading bacteria, antibiotic therapy will be given according to specific indications (Table 12).

DIAGNOSIS

The prescribing of antibiotics for the treatment of urinary infection is still too often haphazard. First, it must be shown that the patient has an infection, and, for this, reliance on examination of a properly collected urine specimen is absolute.

Examination of the Urine

Collection of the specimen for urinalysis in females of all ages must be by aseptic catheterization, and also by this method in males when

TABLE 12. *Antimicrobial Therapy in Urogenital Tract Infections—1956*

	1	2	3	4
INFECTION OR DISEASE	a,g SULFAS TRIPLE OR SULFISOXAZOLE (GANTRISIN)	a,g NITROFURANTOIN (FURADANTIN)	a,f MANDELIC ACID	c,d,e PENICILLIN G
Gram-Negative Bacilli:				
Escherichia coli	B	A	C	
Aerobacter aerogenes	B	C		
Proteus vulgaris	B	B		
Pseudomonas aeruginosa	B	C		
Salmonella- E. typhosa				
B. dysenteriae	B			
B. Friedländer	C			B (4 & 6)
B. Brucella	B			
Gram-Positive Cocci:				
Streptococcus:				
Beta hemolytic	C		C	A (4 & 6)
Alpha hemolytic			C	B (4 & 6)
Faecalis	C		A	A (4 & 6)
Viridans				B (4 & 5; 4 & 6)
Staphylococcus:				
Aureus; Albus	B	C	C	B (4 & 5; 4 & 6)
Pneumococcus				A
Gram-Negative Cocci:				
Gonococcus	B			A
Tuberculosis				
Syphilis				A i
Chancroid				
Lymphogranuloma venereum				B
Granuloma inguinale				
Dose: Grams in 24 hours:				
Infants and Children	0.5–4.0	0.06–0.3	1.0–10.0	0.1–1.0
Adults	2.0–8.0	0.4–0.8	10.0–15.0	1.0–5.0

In severe illness initial doses may be doubled, then reduced to "regular."

Key: A, B, C: indicates order of choice.

Blank spaces mean of little or no value.

Combined therapy if infection severe or resistant shown in parentheses, e.g., (6 & 8—Streptomycin and Achromycin).

a. Oral only.

b. Intramuscular only.

c. Both routes.

TABLE 12. *Antimicrobial Therapy in Urogenital Tract Infections—1956 (Continued)*

5	6	7	8	9	10	11
a ERYTHROMYCIN	b STREPTOMYCIN OR DIHYDROSTREPTOMYCIN	c,d,e,g CHLORTETRACYCLINE (AUREOMYCIN)	c,d,e,g TETRACYCLINE (ACHROMYCIN)	c,d,e,g OXYTETRACYCLINE (TERRAMYCIN)	c,g CHLORAMPHENICOL (CHLOROMYCETIN)	b NEOMYCIN (POLYMYXIN B)
	C, **b** (6 & 8)	B	B	B	B	
	B (6 & 8)	B	A	B	B	
	B				C	B
	B			A(B,6 & 9)	B	A
	B (6 & 1)				B(10 & 1; 9 & 10)	
	B	B	B	B	B	B
		B	B (8 & 10)	B	B	
	B (6 & 8, 9)	B	C	B		
A	B (5 & 6)	B	C	C	C	
A	B	B	C	C	C	
A	B	A	B			
B						
A (0 & 6)	B	B	C	C		
A	C	B	B	B		
A		B	B	B	B	
	A h					
						B
	B	A		B	A	
		A		B	A	
	B	A		B	A	
0.25–1.5	0.05–0.5	0.25–1.5	0.25–1.5	0.25–1.5	0.25–1.5	0.25–1.0
1.0–4.0	0.5–1.5	1.0–5.0	1.0–5.0	1.0–5.0	1.0–5.0	1.0–3.0

d. Oral dose four times and intravenous half the intramuscular dose.
e. May be given intravenously also.
f. As calcium mandelate tablets or syrup equivalent.
g. As capsule, tablet, drops, or suspension equivalent.
h. Combined with PAS (para-aminosalicylic acid) and isoniazid.
i. Use other antibiotics and arsenicals when patient is hypersensitive to penicillin and cannot be desensitized.

"clean-catch" collecting from the voiding stream cannot be properly carried out. For the clean-catch collection the prepuce, when present, is widely retracted and the glans and separated meatus are well cleansed with an antiseptic solution such as oxycyanide of mercury 1:500 or, when this is not at hand, by surgical soap. The male then begins to void, and after a few cubic centimeters have been passed, thereby washing out the urethra, a sterile vessel is introduced into the voiding stream and sufficient specimen is collected for urinalysis and bacteriologic culture. When this collection method cannot be satisfactorily carried out, catheterize. Because of unavoidable contamination the casual voided specimen from the female and from the male with a long constricted prepuce is unreliable for accurate diagnosis, especially bacteriologic, and the findings may be seriously misleading.

In urinary tract infection bacteria are always present in the urine, and pus cells nearly always are. No cell should be identified as a pus cell which does not show the characteristic lobate "pawn broker's" nucleus of the polymorphonuclear leukocyte. Too often epithelial cells and urinary debris are reported as pus. It is of no importance whether the cells are single or clumped; this is merely a matter of numbers. Periodic microscopic examination of the properly collected uncentrifuged specimen will indicate the therapeutic progress. Normally the urine contains a rare leukocyte—not over one to three per low power field—and more than this number would suggest the presence of infection, obstruction, tumor, stone or foreign body.

TREATMENT

Upon determination that the patient has an acute urinary infection, the initial choice of antibiotic or other antimicrobial can be made on the findings from microscopic examination of gram-stained urinary sediment. This will show whether gram-positive cocci or gram-negative bacilli (or both) are present, and the selection of the antimicrobial(s) is made on that basis. Thus one would not give penicillin for coliform bacillary infection, nor Furadantin, for example, for a "pure" coccal infection (see Table 12). On the strength of the gram-stain smear findings, rational antibiotic treatment should be started without delay. Should the culture and sensitivity reports subsequently indicate that another antibiotic should be given, the change can then be made. Lamentably, so much penicillin has been given so injudiciously, unjustifiably and unintelligently these last few years that through bacterial mutation and the acquisition of drug fastness this antibiotic has lost its effectiveness for most of the population at large. Certainly nothing could be better designed to encourage wide drug resistance and

patient sensitiveness to this antibiotic than the indiscriminate use of penicillin lozenges, ointments, salves, suppositories, and the like.

In making the initial choice of antibiotic, the sensitivity tests are of highly suggestive help, but need not be regarded as absolute, clinical experience so often being to the contrary. In short, if an antimicrobial administered to a sick patient on the basis of the sensitivity test proves ineffective, try others, perhaps in combination, even though they may have been shown by test in vitro to be insensitive to the medication. One must still evaluate laboratory reports in correlation with the clinical picture and, when the two disagree, be guided by the clinical observations.

The usual bacterial causes of urinary infection and the antimicrobials which have been found most effective against them are shown in Table 12. Full details of the nature, biology, sensitivities, drug fastness, reactions, tissue damage and antimicrobial effectiveness of these various drugs, singly or in combination with other biotics or chemicals, are given in other clinics in this symposium and need not be repeated here. Suffice it to re-emphasize that the bacterial sensitization tests, usually of great value, are not absolute guides.

Most antimicrobials must be administered for at least 10 days, and if at the end of this time the infection is not eradicated as proved by urine culture—preferably two, a week apart—continue the same medication or switch to another which may seem indicated.

The chief causes of therapeutic failure are (1) ignorance of the type of and drug response to the invading bacteria, (2) improper choice of antimicrobial, (3) drug administration in too small doses and/or for too short a time, and (4) unrecognized or unrelieved urinary stasis or associated conditions such as hydronephrosis, vesical diverticulum, urinary stone or tumor.

In acute urinary infection, failure of satisfactory response to three days of intensive antibiotic treatment demands immediate urologic study. Most often this reveals upper urinary tract blockage, especially at the ureteropelvic junction and with complicating infected hydronephrosis, pyonephrosis, renal carbuncle or, perchance, even perinephric abscess. Failure to achieve cure under these circumstances with antibiotics is not necessarily the fault of the medication, but rather of the unalert physician.

Lack of success in achieving bacteriologic cure of chronic urinary infection with three weeks of intensive medical treatment demands urologic investigation, at least to the extent of a satisfactory excretory pyelographic study and determination of the presence of residual urine in the bladder or renal pelvis. These studies often show that further investigation is necessary, usually by complete examination of the entire

urinary tract and adnexa by cystoscopy, ureteral catheterization, divided renal function tests and bilateral retrograde pyelography. This study in infants and children may reveal any one or more of a large number of urologic conditions which are customarily found in adults; most of them will be obstructive and often with associated disease such as calculi, the formation of which is predisposed to by the urinary stasis and infection. Here treatment demands eradication of the stasis-producing conditions and complicating lesions before intensive antimicrobial therapy can be expected to sterilize the urine. Unless these lesions are eliminated, subsequent recurrence of infection is practically certain; meanwhile the kidneys are insidiously subjected to progressive injury, and often with grave results.

In addition to the antimicrobial therapy outlined, maintenance of the nutrition of the patient and liberal blood transfusion when indicated must not be overlooked. But most of all it is urged that any urinary infection—acute or chronic, nontuberculous or tuberculous—be seriously considered clinically and the large number of potential associated causes of its occurrence and/or persistence be recognized and eradicated. Without this broad approach to and attack upon the disease, the mere prescribing of antibiotics is most likely to be therapeutically futile and a frightful economic waste, and, worst of all, grave tissue damage, especially to the kidneys, progresses. All these considerations are of utmost seriousness when the patient is an infant or child.

520–522 Alfred I. duPont Building
Miami, Florida

MANAGEMENT OF BACTERIAL MENINGITIS IN CHILDREN

M. J. CARSON, M.D.

R. KOCH, M.D.

Management of acute bacterial meningitis has undergone great change during the past two decades, primarily because of availability of increasingly efficient antibiotics. The clinician can confidently expect an over-all recovery rate of approximately 90 per cent, whereas this figure formerly would have approximated 10 to 20 per cent. Reduction of complications has also been striking so that hydrocephalus, blindness, deafness, mental retardation and other neurologic sequelae are uncommon in adequately handled cases. Although specific bactericidal and bacteriostatic agents can be given great credit for these advances, better diagnostic and supportive measures have contributed significantly. As improved therapeutic agents are constantly being developed, periodic review of the problem is necessary.

Table 13 summarizes a 10 year review of various types of nontuberculous, acute purulent meningitis admitted to Los Angeles Children's Hospital from 1944 to 1953.[71] Hemophilus influenzal meningitis was most common, occurring in 106 cases (30 per cent), meningococcal meningitis in 20 per cent, and pneumococcal in 11.6 per cent. *Escherichia coli*, Salmonella, Micrococcus (Staphylococcus), Streptococcus, Pseudomonas, Paracolon and Proteus combined accounted for 7.9 per cent of total cases. These findings emphasize several interesting features. In spite of adequate methods of bacterial identification, the causative organism could not be isolated in 91 cases (26 per cent) presenting a clinical picture of bacterial meningitis. Antibiotic therapy prior to hospitalization is thought to be one of the chief reasons for inability

From The Los Angeles Children's Hospital and The Department of Pediatrics, University of Southern California School of Medicine, Los Angeles.

TABLE 13. *Incidence of Various Types of Acute Purulent Meningitis, 1944–53, at Los Angeles Children's Hospital*

ETIOLOGIC AGENT	NUMBER	PER CENT OF TOTAL
H. influenzae	106	30
Unknown	91	25
N. meningitidis	72	20
D. pneumoniae	41	11.7
E. coli	19	5.4
Micrococcus	6	7.9
Salmonella	6	
Streptococcus	5	
Pseudomonas	5	
Paracolon	2	
Proteus	1	
Total	354	100%

to isolate causative bacteria. The relatively low incidence of pneumococcal meningitis is coincidental with improved therapy of otitis media, marked decrease in mastoiditis, and great sensitivity of pneumococcal infections to penicillin.

CLINICAL SYNDROME

Regardless of organism, central nervous system pathology consists of inflammation of the arachnoid and pia mater with purulent exudate covering the cerebral hemispheres, cerebellum and spinal cord. Superficial cerebral vessels are frequently involved with thrombosis, rupture and hemorrhage. Tissues of the brain are commonly affected with perivascular leukocytic infiltration, hemorrhage and necrosis.

The onset of clinical symptoms is often preceded by respiratory infection, and central nervous system invasion is usually the result of bacteremia, although direct extension from the middle ear through the mastoid process or petrous portion of the temporal bone must always be considered. Hyperpyrexia develops coincident with meningeal involvement frequently accompanied by vomiting, chills and convulsions. Headache is characteristic in older children, followed by increasing lethargy, delirium and coma. Sometimes the patient or parent will spontaneously discover stiffness of the neck or back. Physical examination usually reveals a lethargic, critically ill child who is irritable and frequently disoriented when aroused. Spasm of neck and back muscles is characteristic, and flexion of the neck usually results in flexion of the knees and hips (Brudzinski's sign). Similarly, inability to straighten the knee with the hip flexed is commonly demonstrable (Kernig's sign). Bulging or tenseness of the anterior fontanel is a reliable sign of increased intracranial pressure. Retinal hemorrhages or papilledema is unusual, but occasionally seen. Skin rash must be carefully sought for, since petechial or purpuric lesions are particularly characteristic

of meningococcal infection. Tachycardia, respiratory irregularity, hypotension and cyanosis are indications of severity of infection or degree of toxemia, and serve as a guide to the urgency of vigorous supportive therapy.

Striking as are these manifestations, it must be remembered that some or all may be lacking in the premature and small infant.[39, 74] Here the only indication of disease may be refusal of formula, cyanosis, increasing lethargy, vomiting, respiratory irregularity or hypothermia. Examination may not reveal meningitic signs. Fullness of the anterior fontanel or hydrocephalus may be a late indication of intracranial infection.

DIFFERENTIAL DIAGNOSIS

Etiologic documentation of clinical diagnosis must be made by microscopic and cultural examination of the cerebrospinal fluid. Careful inquiry of close contacts must be made for tuberculous history. Although tuberculous meningitis usually has symptoms extending over one or more weeks, the course may occasionally be rapid and fulminating. The presence of congenital heart disease may suggest the possibility of brain abscess, particularly if the symptoms are of short duration, and papilledema is present. Contact with acute anterior poliomyelitis or history of a prior sore throat and a febrile episode suggests this possibility. Backache, muscle pain or paralysis, urinary retention and hyporeflexia are characteristic of poliomyelitis. Contact with measles, mumps or chickenpox should be explored, since symptoms of acute central nervous system invasion accompany these diseases and may be the only or initial manifestations. If such contact can be substantiated, particularly with other findings such as parotid swelling, typical exanthem of measles or chickenpox, and the like, viral meningoencephalitis is almost certain instead of bacterial meningitis. Equine encephalitis may be suspected in the presence of known infection in nearby horses or in epidemic areas. Coccidioidomycosis usually does not have a rapid, fulminating course, but should always be considered in endemic areas. Brain tumor rarely will present with acute findings suggesting bacterial infection. Careful questioning will almost always disclose symptoms of several weeks' duration, and localized neurologic abnormalities will commonly be present.

Cerebrospinal fluid examination is necessary for definitive diagnosis and must be carried out in every case of suspected meningitis. The fluid should be examined immediately by gross and microscopic inspection, and culture obtained. The gross appearance will indicate the presence of blood, xanthochromia or turbidity. In overwhelming infection, turbidity may be due to tremendous numbers of organisms,

with a low total white blood cell count. The type of cellular response is helpful, for polymorphonuclear cells suggest bacterial meningitis, whereas lymphocytes are more characteristic of viral or tuberculous infection. The striking exception to this generalization is in early tuberculous meningitis or poliomyelitis, in which polymorphonuclear cells may predominate. Glucose concentration is normally about one-half that of blood plasma level. It is characteristically low in purulent and tuberculous infection, and normal in viral infections. Decreased glucose concentration associated with meningeal sarcoma has at times led to mistaken diagnosis of acid-fast infection. Cerebrospinal fluid

TABLE 14. *Cerebrospinal Fluid Changes in Central Nervous System Disease*

	TYPE FLUID		CELL		CHEMISTRY		SMEAR AND CULTURE
	Descript.	Pressure	Count	Type	Protein	Glucose	
Purulent meningitis	Turbid	Inc.	1000–10,000	P	Inc.	Dec. 10–40 mg.	Dependent on organism Quellung pos. H. influenzae
Tuberculous meningitis	Clear or opalesc.	Inc.	15–1000	L	Inc.	Dec. 10–30 mg.	Positive acid-fast
Brain abscess	Clear	Inc.	15–100	L	Inc.	N	Negative. With rupture fluid becomes purulen
Poliomyelitis	Clear, ground-glass	N	15–1000	P (early) L (later)	Inc.	N	Negative
Meningo-enc. (mumps-measles) etc.	Clear, opales.	N	15–1000	L	Inc.	N	Negative
Viral enc.	Clear	N	15–150	L	Inc.	N	Negative
Lymphocytic choriomening.	Clear	N	50–300	L	Inc.	N	Negative
Brain tumor	Clear	N	None Occ. 10–100	L/or tumor	N/or inc.	N	Negative

N: normal; Inc.: increased; Dec.: decreased; L: lymphocytes; P: polymorphonucleara.

protein is elevated in all forms of infection and in general correlates with cellular response. The outstanding exception to this general rule is in cord tumors and the "Guillain-Barré" syndrome, in which protein is elevated without pleocytosis.

Examination of stained smear is of value in bacterial diagnosis. Even in competent hands, however, this method of identification is liable to considerable error and obviously cannot be relied upon to guide specific therapy. The Quellung test for *Hemophilus influenzae*, type "B," is reliable, and a positive test is as certain as cultural identification. Using the combination of stained smear and Quellung test, we have been able to properly identify 75 per cent of influenzal type "B" infections shortly after admission. Table 14 outlines cerebrospinal fluid findings in various infectious diseases of the central nervous system.

HEMOPHILUS INFLUENZAE MENINGITIS

Hemophilus influenzae is a gram-negative, pleomorphic coccobacillus which grows best on chocolate agar under reduced oxygen tension. The strains causing meningitis are serologically related and classified as type "B." This form of meningitis occurs most commonly under four years of age, with a peak incidence between six and 12 months. It is most prevalent during winter months, coincident with highest frequency of respiratory infections. Nasopharyngitis, otitis media and orbital infections commonly precede bacteremia which results in cerebrospinal fluid invasion. Direct extension of infection through temporal bone or cribriform plate is rare.

Presenting symptoms and signs in 128 patients[41] studied are identical to those indicated earlier, consisting of fever, vomiting and lethargy, with convulsions occurring in approximately one fourth of patients. Tense anterior fontanel or positive meningeal signs were present except in very young, moribund infants. Leukocytosis with granulocytosis is demonstrable in peripheral blood examination except in severe, overwhelming infection in which occasional leukopenia is seen. Nasopharyngeal and blood cultures will demonstrate the causative organism in 50 to 75 per cent of cases. The cerebrospinal fluid is purulent with 80 to 90 per cent polymorphonuclears, reduced sugar and elevated protein. Early cases may be seen in which the cerebrospinal fluid is clear with fewer than 20 cells per cubic millimeter, but with positive culture. When the organism is recovered, sensitivity studies are often a guide to specific therapy. All organisms so far tested in our laboratory have proved sensitive to tetracyclines and chloramphenicol. Before specific therapy was available a mortality rate of 90 to 100 per cent was expected.[63] Sulfonamide therapy alone was ineffective;[11, 41, 46, 68] however, when sulfonamide was combined with Alexander's rabbit antiserum, the mortality dropped to 25 to 50 per cent.[1, 3, 11, 24, 41, 46, 52, 68, 79, 82] The mortality rate decreased to 10 per cent with streptomycin[12, 56] and to 5 per cent with use of broad-spectrum antibiotics such as oxytetracycline[41] and chloramphenicol.[19, 49, 60, 63, 64, 66]

MENINGOCOCCAL MENINGITIS

This is due to a gram-negative, biscuit-shaped coccus (*Neisseria meningitidis*) which is usually found endemically, but may occur in epidemics.[77] Review of our 120 cases indicates a peak incidence between three months and two years. Eighty per cent of all cases occur during the first 10 years of life, and are primarily seen during cold weather, particularly from January to April. In contrast to other types of meningitis, familial incidence occurs in 2 per cent of cases, and

family contacts show higher antimeningococcal antibody titers than casual contacts.[78] Males are more frequently affected than females (64 per cent of our series), although the mortality rate in males was one half that of females. Upper respiratory infections precede bacteremia or clinical meningitis in about 50 per cent of cases.

Although there is some variability, the usual clinical picture is abrupt in onset with chills, high fever, vomiting and prostration. Convulsions occur in one quarter of cases, and delirium is common. Petechial, purpuric or maculopapular skin rash develops in 60 per cent of patients, and severe toxemia with peripheral circulatory collapse, cyanosis, respiratory irregularity, coma and death may occur in eight to 48 hours. Purpura may become extensive, resulting in necrosis, sloughing and even gangrene of fingers, toes or portions of extremities. Extensive skin hemorrhage and early onset of circulatory collapse are ominous signs. Patients with a systolic blood pressure of 60 mm. of mercury or below have a 60 per cent mortality rate, in contrast to the remainder with a 10 per cent mortality rate. Remaining signs and symptoms are those common to all forms of purulent meningitis and have been discussed.

Correlation of bilateral adrenal hemorrhage with meningococcemia and meningitis resulted from observations by Waterhouse,[80] McLagan and Cooke[48] and Friderichsen.[28] The Waterhouse-Friderichsen syndrome refers to cases of acute, fulminating meningococcemia with cyanosis, shock and death, which show adrenal hemorrhage. This condition was considered universally fatal until 1940, when Carey[16] reported recovery of a patient treated with sulfonamides. Recent reports of combination of antibacterial agents[10, 13, 27, 32, 35, 36, 37, 54, 55, 81] plus steroid and norepinephrine[53] therapy indicate more optimism in management of this problem. Mortality with sulfonamide therapy is 5 to 10 per cent.[21, 32, 71, 76]

PNEUMOCOCCAL MENINGITIS

In our experience pneumococcal meningitis is the third most common form of purulent meningitis, if one ignores the large group of cases which remain bacteriologically undiagnosed. It is due to a gram-positive diplococcus which grows readily on blood agar and is easily identified by gram stain. Concomitant disease of the respiratory tract such as otitis media, mastoiditis and bronchopneumonia is common. Head injury and sicklemia occasionally are predisposing factors. The peak incidence is during winter, and 60 per cent of patients are under the age of one year. Petechiae are rare, and invariably a white blood cell count elevation of 20,000 to 30,000 with granulocytosis occurs. The cerebrospinal fluid is viscid and contains many polymorphonuclears with low sugar and elevated protein content. The mortality rate

with penicillin and sulfonamide therapy is 16 to 20 per cent.[18, 62, 71] Neurologic sequelae such as hydrocephalus, motor disabilities, deafness and mental retardation as well as recurrence of meningitis are more common in spite of adequate therapy.

MISCELLANEOUS

High mortality rates occur in meningitis due to bacillary and enteric organisms. *Escherichia coli* is the most common form of these and occurs predominantly in the neonate,[39, 71] secondary to bacteremia, omphalitis, spinal canal anomalies or genitourinary uropathy. Enteric infections may be preceded by diarrhea.[47, 72] Streptococcal meningitis has become rare, owing to great sensitivity of the organism to penicillin. Staphylococcal meningitis commonly occurs as a secondary phenomenon.[71] Syphilitic and fungal infections such as coccidioidomycosis and torulosis are rare.

CLINICAL MANAGEMENT

Optimal management may be discussed under the following categories: (1) early diagnosis, (2) general supportive measures, (3) specific antibacterial therapy, (4) recognition and treatment of complications.

Early Diagnosis

Criteria for diagnosis have already been reviewed, and increased mortality and permanent sequelae resulting from deferred diagnosis and inadequate therapy are too well known to warrant further discussion. With the physician's high index of suspicion confirmed and the diagnosis of meningitis established, definitive procedures are immediately instituted.

General Supportive Measures

Fluid therapy and supportive measures are basically the same as for any critically ill child. As varying degrees of dehydration, ketosis or acidosis may be present, they must be evaluated clinically and by laboratory. Infants ill with infection for one to three days have water deficits due to decreased fluid intake, vomiting and increased insensible loss. Marked electrolyte deficits are unusual, but ketosis and acetonuria are to be expected. Plasma carbon dioxide is slightly reduced with essentially normal plasma chlorides. If carbon dioxide is below 15 milliequivalents per liter, the plasma pH is almost certainly decreased

and true metabolic acidosis exists. Minimal to moderate dehydration represents 5 to 10 per cent body water loss. Intravenous 5 per cent glucose and Ringer's lactate solution is a good initial combination, but sixth-molar lactate may be needed if the plasma carbon dioxide is below 15 milliequivalents per liter. Overhydration must be avoided to prevent aggravation of cerebral edema which may lead to convulsions and respiratory irregularity. This same condition may be produced if only nonelectrolyte-containing fluids are used, even though the total quantity is not excessive. Anemia is corrected after initial hydration by appropriate amounts of whole blood. Sponging, cooling enemas, judicious use of salicylate and the cool environment of an oxygen tent will reduce hyperpyrexia. Oxygen per se is of little value unless cyanosis or respiratory irregularity is present. Constant nursing care is essential with frequent turning and adequate suctioning of the nasopharynx. Oral fluids and medication should not be offered during the initial, critical 24 to 48 hours because of possible vomiting and aspiration. Management of convulsions must be prompt but conservative. Phenobarbital, paraldehyde and chloral hydrate will usually suffice. The latter two drugs are particularly valuable because of lack of depression of the respiratory center. If convulsions are severe and refractory to treatment, subdural effusion, cerebral edema and cerebral vascular involvement must be considered. Subdural taps will localize and drain the effusion, and hypertonic glucose solution may temporarily alleviate the symptoms of cerebral edema. Daily cerebrospinal fluid examination is unnecessary, but repeat examinations should be done on the fourth day of therapy to verify clearing of the fluid. Final cerebrospinal fluid check before discharge should be routine.

Specific Antibacterial Therapy

Although improvement in the patient recovery rate resulted from use of specific antiserums against meningococcal[58] and influenzal infections,[3, 41] greatest improvement has resulted from the use of sulfonamides and antibiotics.[8, 20] Figures 8 and 9 correlate reduction of mortality rate and percentage of complications with varying therapeutic programs. Figure 8 clearly shows the persistence of a high percentage of complications in influenzal meningitis until addition to therapy of the broad-spectrum antibiotic, oxytetracycline. Figure 9 is of interest in that the mortality rate in meningococcal meningitis has not changed significantly since the introduction of sulfonamides.

The multiplicity of available antibiotics is frequently confusing, but choice of an agent must satisfy the following criteria: (1) It must be effective against the causative organism in concentrations which can be achieved in body fluids and not be toxic to body tissues. (2) A

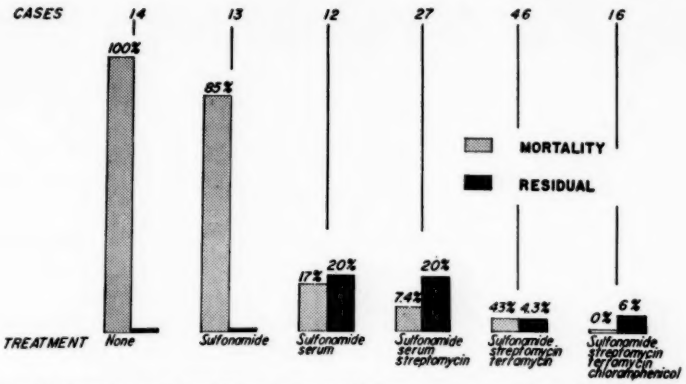


Fig. 8. Correlation of reduction of mortality rate and percentage of complications in 128 cases of *Hemophilus influenzae* meningitis treated at Los Angeles Children's Hospital with varying therapeutic programs from 1930 to 1953. (Authors' article in *J. Pediat.*, Vol. 46, published by C. V. Mosby Company.)

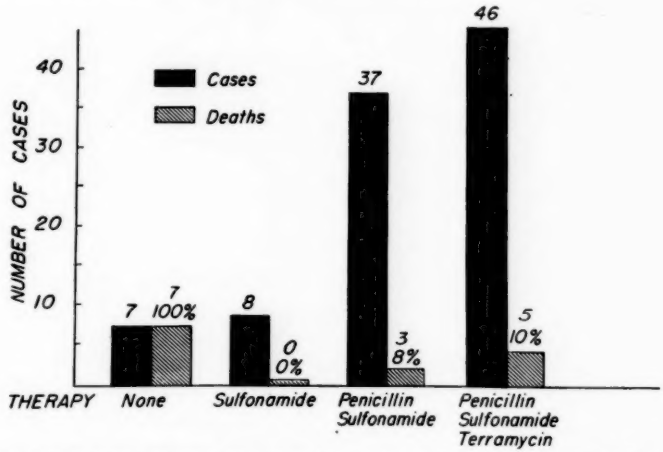


Fig. 9. Correlation of mortality rate with varying therapeutic programs in 98 cases of meningococcal meningitis treated at Los Angeles Children's Hospital from 1934 to 1954.

satisfactory parenteral preparation must be available. (3) Combination of drugs with different modes of action is desirable to prevent development of bacterial resistance.

Table 15 lists drugs with their action on bacteria commonly encountered in meningitis. Sulfadiazine is bacteriostatic and may be administered subcutaneously in 0.5 to 5.0 per cent solution with Ringer's-lactate solution in dosage of 0.1 gm. per kilogram every 12

hours. This produces a plasma level of 10 to 15 mg. per 100 ml., of which 60 per cent will diffuse into the cerebrospinal fluid. Renal complications are unlikely if adequate urine volume is maintained and the urine pH is maintained at 7.0 or above. Other undesirable manifestations such as drug fever or hematopoietic complications are rarely seen before the second week of therapy. Alexander and associates demonstrated delay in emergence of bacterial resistance to streptomycin when combined with sulfadiazine.[4, 5]

Streptomycin is bactericidal in concentrations of 10 micrograms per cubic centimeter.[6] It is best given intramuscularly, readily diffusing throughout body fluids. Its mechanism of action differs from that of both sulfonamides[2] and tetracycline.[7] Maximal bactericidal effect and

TABLE 15. *Bacterial Sensitivity to Drugs Commonly Used in Meningitis*

	SULFADIAZINE	PENICILLIN	STREPTOMYCIN	CHLORAMPHENICOL	OXYTETRACYCLINE	TETRACYCLINE	ERYTHROMYCIN
H. influenzae	?	O	X	X	X	X	O
N. meningitidis	X	X	O	X	X	X	?
D. pneumoniae	X	X	O	X	X	X	X
Streptococcus	X	X	O	X	X	X	X
E. coli	X	O	X	X	X	X	O
Salmonella	O	O	?	X	X	X	O
Micrococcus (staphylococcus)	X	X	O	X	X	X	X

X: most effective agents; X: effective; O: ineffective; ?: questionable efficiency.

increasing bacterial resistance occur rapidly, so that its main value is during the first few days of application. Vestibular damage and deafness usually result from prolonged therapy, but vestibular damage has been reported by Alexander[2] following one intrathecal dose and intramuscular injections for only 24 hours. We have used the intramuscular route exclusively during the past six years and have seen only one patient who had mild transient vestibular damage.

Penicillin is bactericidal against sensitive bacteria. Adequate levels in plasma and body fluids are easily achieved except in cerebrospinal fluid,[61, 62] which, however, is increased in the presence of inflamed meninges. Intramuscular, intravenous and subcutaneous routes of administration are preferred, and oral use must not be relied upon. Toxicity is slight, although intravenous use of large doses has resulted in convulsions and respiratory failure.[42]

Chloramphenicol, oxytetracycline and tetracycline have been studied and shown to be bacteriostatic in action. Each is effective against organisms, as indicated in Table 15. They may be safely administered orally, intravenously and intramuscularly with effective plasma and

body fluid levels easily obtained. In the normal patient chloramphenicol[19] diffuses into cerebrospinal fluid in greater quantity than either oxytetracycline or tetracycline. However, with meningeal inflammation cerebrospinal fluid levels of these latter two are significantly increased to 5 and 3 micrograms per cubic centimeter, with corresponding plasma levels up to 40 and 24 micrograms per cubic centimeter respectively.[15, 43] Most sensitive bacteria respond to levels of 0.1 to 0.5 microgram. Toxicity of oxytetracycline and tetracycline has been slight with infrequent nausea, vomiting and diarrhea. Thrombophlebitis results from prolonged intravenous use and cellulitis from frequent intramuscular injections into the same site. No evidence of hematopoietic damage has been noted. Chloramphenicol[17, 23, 26, 30, 34, 44, 57, 69, 70, 83, 84, 85] used in short courses of treatment in our hospital has not resulted in hematopoietic damage, but there is considerable evidence this is a potential danger and must be constantly kept in mind.

Use of multiple agents for rapid eradication of infection is then based on utilization of several drugs with different mechanisms of action to achieve rapid bactericidal and bacteriostatic effect, and to prevent development of bacterial resistance. Possibility of antibiotic antagonism as indicated by laboratory studies of Jawetz and co-workers[33, 38] has been further explored by others with final conclusions that this observation is not clinically significant when large doses are being used. Additional work emphasizes the importance of combinations of antibiotics delaying emergence of bacterial resistance.[25, 86] There now seems clear evidence for use of multiple drug therapy.

When faced with the usual case of meningitis, an etiologic diagnosis cannot always be made with certainty by examination of the patient and stained smear of the cerebrospinal fluid (excluding evident meningococcemia with widespread purpura). Even in competent hands examination of the cerebrospinal fluid gram stain is not absolutely reliable. With the exception of the Quellung test for *H. influenzae* type "B," bacterial identification must frequently await culture, which necessitates 24 to 48 hours' delay. In unknown cases correct therapy must be immediately instituted, and under these circumstances our method of therapy is immediate, energetic and inclusive. Intravenous infusion of indicated fluids is begun by cut-down or lay-in procedures. Oxytetracycline or tetracycline is given intravenously in four equally divided doses amounting to 75 mg. per kilogram per day. Aqueous intramuscular penicillin, 200,000 to 300,000 units every three hours, and intramuscular streptomycin, 50 mg. per kilogram daily, are given in divided dosage every 12 hours. Sodium sulfadiazine is given subcutaneously, 0.2 to 0.3 gm. daily, in four equally divided doses, usually in Ringer's lactate or sixth-molar sodium lactate solution as needed. This general plan is maintained until cultural identification of the bacteria

is obtained. With this vital information the least effective drugs are eliminated.

If *Meningococcus* is found, only penicillin and sulfadiazine are continued. With sufficient improvement in one to two days, parenteral sulfadiazine is changed to oral triple sulfonamide, 0.3 gm. per kilogram daily. Aqueous penicillin is changed to the procaine form, 300,000 to 600,000 units every 12 hours. Therapy is gradually decreased and discontinued after seven days of normal temperature. During vigorous sulfonamide therapy, daily examination of urinary sediment and pH will detect earliest signs of renal damage. Sulfadiazine plasma levels should be ascertained during the first critical days, and the peripheral

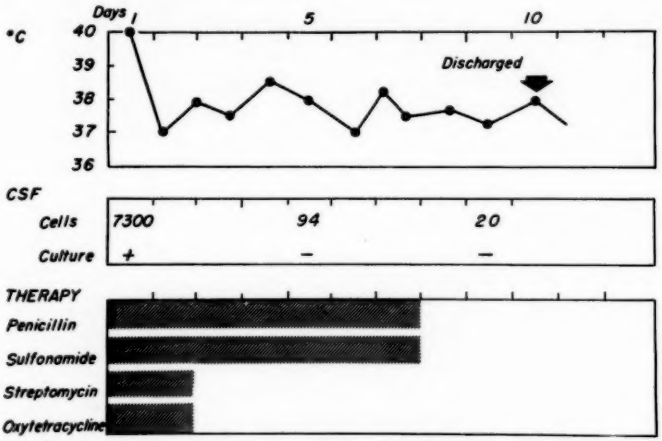


Fig. 10. The course of one of the representative uncomplicated cases of meningococcal meningitis treated with sulfonamides and penicillin.

white blood cell count and differential should be checked weekly. If hematuria develops because of sulfonamides, alkalinization of urine and adequacy of urine formation should be verified and carried out. No harmful effects from sulfonamides have been noted in our cases. Sulfonamide prophylaxis for other family members is routine with meningococcal infections. Figure 10 depicts the course of one of the representative uncomplicated cases in our series. With therapy as outlined, recurrence has not been noted and the mortality rate in 91 treated cases is 8.8 per cent.

If *H. influenzae*, type "B," is identified by culture, penicillin is discontinued and streptomycin is continued until the third to fifth day of therapy. Sulfonamides are continued for one week and oxytetracycline or tetracycline continued until the temperature has been normal for seven to 10 days. This antibiotic is given intravenously for the first

two to four days and then changed to oral administration. Intramuscular use is to be avoided if possible because of cellulitis and sterile abscess formation.[42] If used, the concentration should not be greater than 50 mg. per cubic centimeter, given deeply in the muscle every eight hours with the sites of injection constantly rotated. With this therapy we have had no recurrences and from 1948 through 1953 had only two deaths in 62 cases.[41] Figure 11 depicts the clinical response of a typical uncomplicated case.

In dealing with pneumococcal meningitis one is still faced with high mortality in spite of adequate antibacterial agents.[71] Mortality rates are 10 to 40 per cent[14, 22, 29, 45, 62] in comparison to 10 per cent in

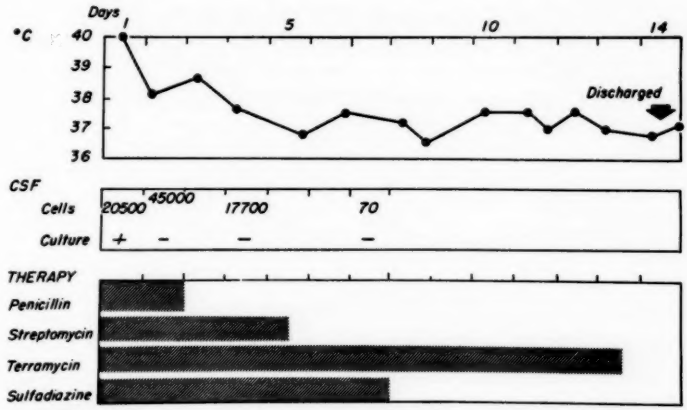


Fig. 11. Clinical response of a typical uncomplicated case of *Hemophilus influenzae* meningitis treated with streptomycin, Terramycin and sulfadiazine.

meningococcal (Fig. 9) and 7 per cent in influenzal infections.[41] The reasons for this are not clear. It may be that pneumococcal meningitis usually has a focus of infection in the mastoid, sinuses or middle ear or is related to head injury. These foci of infection with viscid exudate may form a source of continuing production of organisms in spite of good plasma penicillin and sulfonamide levels. For this reason this type of meningitis should be treated vigorously and for a prolonged period, three weeks being the minimum treatment period. Aqueous penicillin in dosage of 1 to 2 million units should be given every three hours intramuscularly. Sulfadiazine therapy is similar to that outlined for meningococcal infections. If the patient is doing well, tetracycline may be discontinued when the culture is reported. Foci of infection should be eradicated. If otitis media is present, myringotomy should not be delayed, and simple mastoidectomy should be done if mastoiditis is present, but only when the patient has improved.

Intrathecal penicillin therapy has not been used in our hospital in 41 cases of pneumococcal meningitis with a 14.6 per cent mortality rate. Others routinely use intrathecal penicillin,[2, 22, 62] especially in pneumococcal meningitis, because penicillin does not readily cross the blood-cerebrospinal fluid barrier.[22, 61, 62] The advantage of initial intrathecal instillation of 5000 or 10,000 units of penicillin is production of high therapeutic antibiotic level at the site of infection.[22] One instillation of 5000 units maintains therapeutic concentrations in the cerebrospinal fluid for 24 to 30 hours.[61] Our mortality figures without intrathecal therapy compare favorably with those series in which it was used.

In therapy of patients without a bacterial diagnosis we follow the regimen outlined for treatment of *H. influenzae* meningitis. For *E. coli*, Salmonella, Proteus, Micrococcus and Pseudomonas infections, sensitivity tests should be done to help guide therapy. Salmonella may respond to streptomycin, chloramphenicol or tetracycline.[72] Pseudomonas infection can sometimes be controlled with polymyxin.[40] Micrococcal (staphylococcal) infections in our hospital are most often sensitive to erythromycin or chloramphenicol.

Steroid therapy should be reserved for acute fulminating meningococcemia, and its routine use is unwarranted.

RECOGNITION AND TREATMENT OF COMPLICATIONS

Management of Subdural Effusion

In 1916 an association between meningitis and subdural hematoma was suspected by Schwartz,[65] who reported a case of meningococcal meningitis complicated by hydrocephalus due to subdural hematoma. In 1923 Penfield[59] reported the case of a 16 months old infant with subdural effusion who had been seriously ill at seven months with fever, vomiting and purulent otitis media, but with spontaneous recovery. He attributed this to undiagnosed meningitis or mastoid infection. McKay and Ingraham[50] describe subdural effusion as a loculated collection of fluid within the arachnoid between the dura and pia mater. It is usually bilateral, occurring over the frontoparietal area of the cortex. Characteristics of this fluid have been independently investigated by Arnold[9] and Gitlin,[31] who have shown that the proteins originate from the blood. Arnold[9] has found the yellow pigment derived from the heme portion of the hemoglobin molecule. In 1945 Spitz[75] suggested three possible modes of origin for postmeningitic subdural effusion: (1) direct extension through the arachnoid membrane, (2) infection of bridging veins with septic thrombi with secondary thrombosis and stasis, (3) simultaneous infection of the

arachnoid and dura by blood-borne infection. The third possibility seems logical because bacteremia occurs in these patients and the character of the effusion fluid differs. It may be clear without cellular elements, or grossly purulent. Hemorrhagic elements may or may not be present. Gitlin[31] measured albumin concentration of the subdural fluid in 18 cases with different etiologic mechanisms and found uniform elevation compared with albumin concentration of the blood. He feels that the mechanism of subdural effusion is identical in all types.

In 1950 and 1951 McKay[51] and Smith[73] reported the first sizable series of postmeningitic subdural effusions. McKay[51] reported an incidence of about 60 per cent under one year of age, and Smith[73] about 50 per cent in all cases of purulent meningitis. The incidence of postmeningitis subdural effusion in our hospital was only 23 per cent from 1952 to 1953,[67] nine cases in influenzal meningitis, four in meningococcal and six in pneumococcal.

Subdural taps are not performed routinely. Specific indications are the following: prolonged fever, persistent vomiting, continued focal convulsions, bulging of the anterior fontanel without decompression following spinal tap, hemiparesis and continued irritability with anorexia. Occasionally a difference in percussion note of the skull can be detected if the effusion is unilateral, the sound being higher pitched over the fluid collection. The electroencephalogram is helpful in localizing unilateral subdural fluid, since brain wave potentials over the affected side are markedly diminished.

Therapy of subdural effusion has not been standardized. In Boston[51] craniotomy procedures are done more or less routinely. At the Charity Hospital in New Orleans[73] craniotomy is resorted to only when repeated tapping of the effusion is unsuccessful. We have followed the latter course, and 14 of our 19 cases have responded to needle aspiration. Only four have required craniotomy for elimination of subdural effusion and removal of membranes. Burr holes with drainage were successful in one case. Figure 12 depicts the clinical course of a patient with bilateral subdural effusions exhibiting prolonged fever and irritability with improvement following aspiration. Operation with removal of membrane was accomplished at a later date. Membrane formation is more likely to occur if the subdural fluid contains numerous polymorphonuclear cells. If one is not careful, secondary infection can occur by contamination, and appropriate antibiotic therapy must be instituted.

The subdural space is tapped with a short, ½-inch, 20-gauge needle equipped with a removable stylet, inserted through the coronal suture, lateral to the anterior fontanel. It has been our practice to drain alternate sides daily, removing as much of the fluid as possible up to

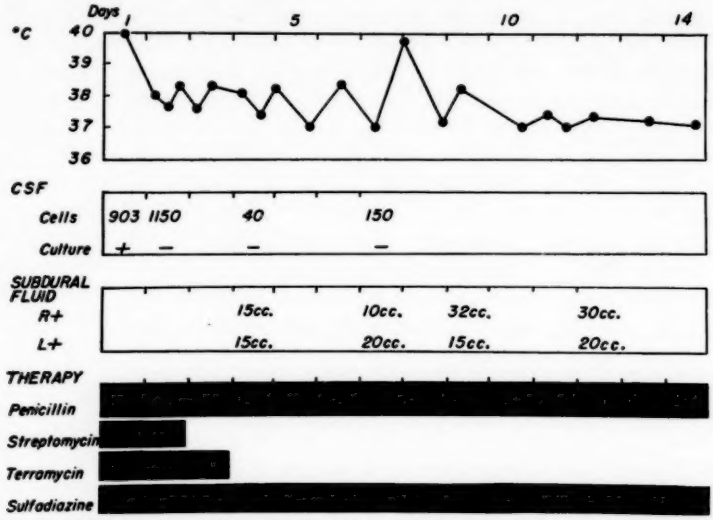


Fig. 12. Clinical course of a patient with meningococcal meningitis complicated by bilateral subdural effusion treated with penicillin and sulfadiazine.

30 cc. Continued convulsions and persistence of large amounts of fluid are indications for neurosurgical intervention.

Waterhouse-Friderichsen Syndrome

These critically ill patients are usually easily recognized by extreme rapidity of course with symptoms and findings as described previously. This is a grave emergency, and therapy must be immediate, adequate and orderly. Necessary diagnostic studies are obtained and intravenous therapy begun. Fluids for the initial 12 hours should be planned to total 5 to 10 per cent of body weight, dependent upon the degree of dehydration. Electrolytes and glucose should be administered together. A mixture of approximately 40 per cent as hypotonic Ringer's, plus 60 per cent as 10 per cent glucose solution in water results in a weak electrolyte-glucose solution which should be easily handled by the cardiac and renal systems. Adrenal cortical extract, neosynephrine and Levophed in strength of 4 mg. per 1000 ml. or greater may be necessary to combat hypotension. Whole blood is valuable and should be incorporated into the total fluid schedule as soon as available. Intravenous hydrocortisone is utilized in doses of 2.5 mg. per kilogram each 24 hours, divided into three equal doses at eight hour intervals. Nasogastric suction, oxygen, cooling measures and excellent nursing care are other essentials. When renal function is definitely established,

potassium lactate should be incorporated into parenteral fluids in the amount of 3 milliequivalents per kilogram each 24 hours to prevent hypokalemia.

Specific antibacterial therapy is essential to destroy bacteria as quickly as possible. Intravenous penicillin provides rapid bactericidal effect in amounts of 500,000 to 2,000,000 units initially, followed by intermittent intramuscular injections as indicated earlier. Intravenous sodium sulfadiazine provides rapid bacteriostasis and is used in amounts previously outlined. Careful judgment must be exercised to prevent overtreatment. Cerebral edema, pulmonary edema and cardiac failure

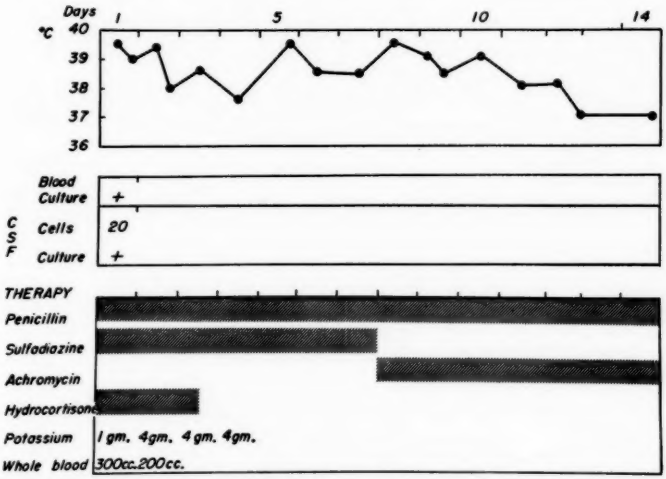


Fig. 13. The course of acute fulminating meningococcemia treated with penicillin, sulfadiazine and Achromycin, with subsequent necrosis and infection of skin and subcutaneous tissues.

may result from too much fluid or use of electrolyte-free solutions. Hypokalemia, hypochloremia and elevated carbon dioxide (metabolic alkalosis) will result with steroid therapy unless potassium is given in adequate amounts.

We have not found it necessary to continue hydrocortisone over 36 to 48 hours. Dosage is halved on the second day and usually discontinued on the third. This plan has been utilized in four survivors of the last seven patients with acute fulminating meningococcemia. Figure 13 demonstrates the course of a patient surviving with acute fulminating meningococcemia with toxemia, cyanosis and hypotension. Subsequent sloughs with secondary infection occurred which responded to addition of Achromycin to therapy.

Autopsy records from 1934 to 1955 show 15 cases of Waterhouse-

Friderichsen syndrome due to Meningococcus. Twelve had massive bilateral adrenal hemorrhage, one had microscopic adrenalitis, and two had normal adrenals. It is of interest that six of the 15 cases were misdiagnosed clinically, the true nature of the disease being discerned only at autopsy. None received specific therapy. Two cases diagnosed as pneumonia were without cutaneous rash, two were thought to have measles and two allergic purpura. Four deaths occurred in patients receiving steroid therapy who showed massive adrenal hemorrhage at autopsy.

Superinfection

In 1953 a 2½ year old white child was admitted with influenzal meningitis. She was treated with sulfadiazine by clysis, Terramycin intravenously and intramuscular

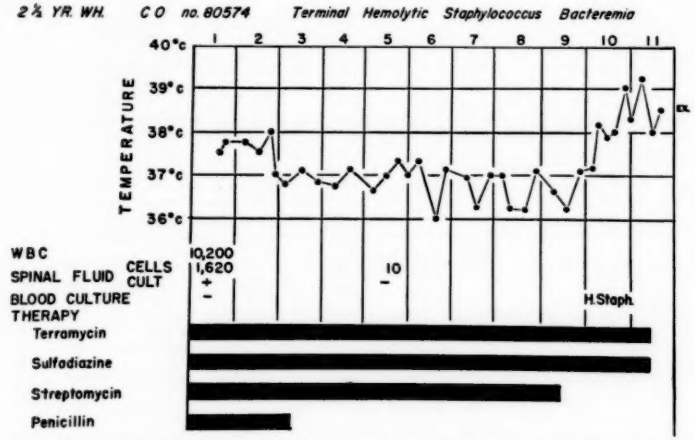


Fig. 14. The clinical course of a fatal hemolytic staphylococcal bacteremia superimposed on a case of *Hemophilus influenzae* meningitis treated with Terramycin, sulfadiazine and streptomycin. (Authors' article in *J. Pediat.*, Vol. 46, published by C. V. Mosby Company.)

streptomycin with rapid improvement. On the ninth hospital day she became ill with nausea and vomiting; on the tenth day she became febrile, and expired on the eleventh day with abrupt onset of circulatory collapse. She was given ACTH without benefit. Premortem blood culture and postmortem cultures of the spleen, respiratory and gastrointestinal tracts revealed *Micrococcus pyogenes* species *aureus*, coagulase-positive. This case has been reported in greater detail elsewhere.[41] Figure 14 details her clinical course. The organism was resistant to drugs used in initial therapy. This complication of broad-spectrum antibiotic therapy has been reported in treatment of other diseases and constantly must be kept in mind.

Cerebral Edema

This complication occurs in a small group of children with severe fulminating meningitis in which the clinical course is rapid and hypo-

tension, cyanosis and respiratory irregularities quickly develop. On examination the eyeballs are usually rotated upward, and papilledema may be present. Initially the respiratory rate is increased, but with imminent death becomes Cheyne-Stokes in nature and then ceases. The heart usually continues to beat for a few minutes to hours if artificial respiration is instituted.

It is in this group of patients that antibiotic therapy alone is not lifesaving. Renal output must be closely watched, and frequent blood electrolyte determinations are essential. Respiratory care with tracheotomy should be used if necessary. Hypertonic glucose is of value in decreasing cerebral edema, and steroid therapy is used for its anti-inflammatory action. If one can tide these patients over the initial critical illness, complete recovery usually ensues.

REFERENCES

1. Alexander, H. E.: Treatment of Purulent Meningitis. *Adv. in Pediatrics*, 2:143, 1947.
2. Alexander, H. E.: Advances in the Treatment of Bacterial Meningitis. *Adv. in Pediatrics*, 5:13, 1952.
3. Alexander, H. E.: Treatment of Type "B" H. Influenzal Infections and of Meningococcic and Pneumococcic Meningitis. *Am. J. Dis. Child.*, 66:172, 1943.
4. Alexander, H. E., and Leidy, G.: Present Status of Treatment for Influenzal Meningitis. *Am. J. Med.*, 2:457, 1947.
5. Alexander, H. E., Leidy, G., Pake, G., and Donovick, R.: Hemophilus Influenza Meningitis Treated with Streptomycin. *J.A.M.A.*, 132:434, 1946.
6. Alexander, H. E., Leidy, G., Redman, W., and Simakov, S.: Experimental Basis for Prediction of Therapeutic Efficacy of Streptomycin in Infections Caused by Gram Negative Bacilli. *Pediatrics*, 5:78, 1950.
7. Alexander, H. E., Leidy, G., and Redman, W.: Comparison of Action of Streptomycin, Polymyxin B, Aureomycin and Chloromycetin in *H. Pertussis, H. Parapertussis, H. Influenzae* and Five Enteric Strains of Gram Negative Bacilli. *J. Clin. Investigation*, 28:876, 1949.
8. Appelbaum, E., and Nelson, J.: Sulfadiazine and Its Sodium Compound in Treatment of Meningococcic Meningitis and Meningococcemia. *Am. J. M. Sc.*, 207:492, 1944.
9. Arnold, G. G.: The Nature of Post Meningitic Subdural Effusions. *J. Pediat.*, 40:757, 1952.
10. Baumann, F., Pearson, D. E., and Levin, M.: Adrenal Cortical Steroids in Management of a Case of Meningococcemia. *J. Pediat.*, 43:575, 1953.
11. Beck, K. H., and Janney, F. R.: Alexander's Rabbit Serum in the Treatment of Influenzal Meningitis. *Am. J. Dis. Child.*, 73:317, 1947.
12. Birmingham, J. R., Kaye, R., and Smith, M. H. D.: Streptomycin in the Treatment of Influenzal Meningitis. *J. Pediat.*, 29:1, 1946.
13. Breen, G. E., Emond, R. T. D., and Walley, R. V.: Waterhouse-Friderichsen Syndrome Treated with Cortisone; Report of 2 Cases. *Lancet*, 1:1140, 1952.
14. Bunn, P. A., and Peabody, G.: Treatment of Pneumococcal Meningitis with Large Doses of Penicillin: Series of 208 Consecutive Cases. *Arch. Int. Med.*, 89:736, 1952.
15. Carson, M. J., and Hansen, H.: Personal observations.
16. Carey, T. N.: Adrenal Hemorrhage with Purpura and Septicemia with Recovery, Case Report. *Ann. Int. Med.*, 13:1740, 1940.

17. Claudon, D. B., and Holbrook, A. A.: Fatal Aplastic Anemia Associated with Chloramphenicol Therapy. *J.A.M.A.*, 149:912, 1952.
18. Daisley, G.: Pneumococcal Meningitis: Special Report. *Clin. Proc. Child. Hosp.*, Washington D.C., 7:1, 1950.
19. Deane, G. E., Furman, J. E., Bentz, A., and Woodward, T. E.: Treatment of Meningitis with Chloromycetin Palmitate. *Pediatrics*, 11:368, 1953.
20. Dingle, J. H., and Finland, M.: Diagnosis, Treatment and Prevention of Meningococcic Meningitis, with Résumé of Practical Aspects of Other Acute Bacterial Meningitides. *War Med.*, 2:1, 1942.
21. Dingle, J. H., Thomas, L., and Morton, A. R.: Treatment of Meningococcemia with Sulfadiazine. *J.A.M.A.*, 116:2666, 1941.
22. Dowling, H. F., Sweet, L. K., Robinson, J. A., Zeller, W. W., and Hirsch, H. L.: The Treatment of Pneumococcal Meningitis with Massive Doses of Systemic Penicillin. *Am. J. M. Sc.*, 217:149, 1949.
23. Editorial: Blood Dyscrasia Following the Use of Chloramphenicol. *J.A.M.A.*, 149:840, 1952.
24. Edmonds, A. M., and Neter, E.: Appraisal of Treatment of Hemophilus Influenza Type "B" Meningitis with Specific Rabbit Serum and Sulfonamides. *J. Pediat.*, 28:462, 1946.
25. Eisenberg, G. M., and O'Loughlin, J. M.: Bacterial Susceptibility to Antibiotics. *Am. J. Clin. Path.*, 23:1040, 1953.
26. Erslev, A.: Hematopoietic Depression Induced by Chloromycetin. *Blood*, 8:170, 1953.
27. Fowler, J. T.: Waterhouse-Friderichsen Syndrome: Recovery of a Patient Treated with Cortisone. *California Med.*, 75:369, 1951.
28. Friderichsen, C.: Neben Nierenapoplexie bei Kleinend. *Jahrb. f. Kindern*, 87: 109, 1918.
29. Gibson, C. D., and James, D. G.: Treatment of Pneumococcal Meningitis since the Introduction of Penicillin. *Lancet*, 2:1203, 1952.
30. Gill, P. F.: Granulocytopenia Following "Chloromycetin": Report of Two Cases. *M. J. Australia*, 1:768, 1950.
31. Gitlin, D.: Pathogenesis of Subdural Collections of Fluid. *Pediatrics*, 16:345, 1955.
32. Griffin, J. W., and Daeschner, C. W.: Meningococcal Infections, with Particular References to Fulminating Meningococcemia (Waterhouse-Friderichsen Syndrome) Treated with Cortisone and Norepinephrine. *J. Pediat.*, 45:264, 1954.
33. Gunnison, J. B., Coleman, Y. R., and Jawetz, E.: Interference of Aureomycin and Terramycin with Action of Penicillin in Vitro. *Proc. Soc. Exper. Biol. & Med.*, 75:549, 1950.
34. Hargraves, M. M., Mills, S. D., and Heck, F. J.: Aplastic Anemia Associated with Administration of Chloramphenicol. *J.A.M.A.*, 149:1293, 1952.
35. Harvey, H. P. B.: A Case of Waterhouse-Friderichsen Syndrome with Recovery Following Use of Cortisone Aqueous Adrenal Cortical Extract and Chemotherapy. *M. J. Australia*, 1:222, 1952.
36. Hodes, H. L., Moloshok, R. E., and Markowitz, M.: Fulminating Meningococcemia Treated with Cortisone: Use of Blood Eosinophile Count as a Guide to Prognosis and Treatment. *Pediatrics*, 10:138, 1952.
37. Jastzeiuski, B., and Hoyt, J. C.: Fulminating Purpuric Meningococcemia. *U.S. Armed Forces M. J.*, 3:769, 1952.
38. Jawetz, E., Gunnison, M. A., and Speck, R. S.: Antibiotic Synergism and Antagonism. *New England J. Med.*, 245:966, 1951.
39. Kagan, B. M., Hess, J. H., Mirman, B., and Lundeen, E.: Meningitis in Premature Infants. *Pediatrics*, 4:479, 1949.
40. Kagan, B. M., Krevsky, D., Milzer, A., and Locke, M.: Polymyxin B and Polymyxin E. Clinical and Laboratory Studies. *J. Lab. & Clin. Med.*, 37:402, 1951.
41. Koch, R., and Carson, M. J.: Management of Hemophilus Influenzal Type B Meningitis. *J. Pediat.*, 46:18, 1955.
42. Koch, R.: Personal observation.

43. Koch, R.: Oxytetracycline Serum and Cerebrospinal Fluid Levels in Meningitis, in *Antibiotics Annual, 1954–55*. New York, Medical Encyclopaedia, Inc., pp. 908–910.
44. Krakoff, I. H., Karnofsky, D. A., and Burchenal, J. H.: Effects of Large Doses of Chloramphenicol on Human Subjects. *New England J. Med.*, 253:7, 1955.
45. Lepper, M. H., and Dowling, H. F.: Treatment of Pneumococcal Meningitis with Penicillin as Compared with Penicillin and Aureomycin. *Arch. Int. Med.*, 88:849, 1951.
46. Levison, A.: Treatment of Influenzal Meningitis. *Illinois Med. J.*, 94:227, 1948.
47. Levison, A., Kadison, E. R., and Diamond, J. H.: Salmonella Typhimurium Meningitis: Report of Two Cases and Review of the Literature. *Am. J. Dis. Child.*, 80:290, 1950.
48. MacLagan, P. W., and Cooke, W. E.: Fulminating Type of Cerebrospinal Fever. *Lancet*, 2:1054, 1916.
49. McCrumb, F. R., and others: Treatment of Hemophilus Influenzae Meningitis with Chloramphanicol and Other Antibiotics. *J.A.M.A.*, 145:469, 1951.
50. McKay, R. J., Jr., Ingraham, F. D., and Matson, D. D.: Subdural Fluid Complicating Bacterial Meningitis. *J.A.M.A.*, 152:387, 1953.
51. McKay, R. S., Jr., Morisette, R. A., Ingraham, F. D., and Matson, D. D.: Collection of Subdural Fluid Complicating Meningitis Due to Hemophilus Influenzae Type B. *New England J. Med.*, 242:20, 1950.
52. McMorrow, K. J., and Top, F. H.: Treatment of Hemophilus Influenzal B. Meningitis. *Pediatrics*, 5:452, 1950.
53. Moyer, J. H., Skeleton, J. M., and Mills, L. C.: Norepinephrine: Effect in Normal Subjects; Use in Treatment of Shock Unresponsive to Other Measures. *Am. J. Med.*, 15:330, 1953.
54. Nelson, J., and Goldstein, N.: Nature of the Waterhouse-Friderichsen Syndrome; Report of a Case with Successful Treatment with Cortisone. *J.A.M.A.*, 146:1193, 1951.
55. Newman, L. R.: Waterhouse-Friderichsen Syndrome: Report of a Cure Effected with Cortisone. *J.A.M.A.*, 146:1229, 1951.
56. Nussbaum, S., Goodman, S., Robinson, C., and Ray, L.: Influenzal Meningitis. *J. Pediat.*, 29:14, 1946.
57. Osgood, E. E.: Hypoplastic Anemia and Related Syndrome Caused by Drug Idiosyncrasy. *J.A.M.A.*, 152:816, 1953.
58. Parmelee, A. H.: Epidemic Cerebrospinal Meningitis. *J.A.M.A.*, 60:659, 1913.
59. Penfield, W. G.: Subdural Effusion and Internal Hydrocephalus: Study of a Case with Recovery. *Am. J. Dis. Child.*, 26:383, 1923.
60. Prather, G. W., and Smith, M. H. D.: Chloromycetin in the Treatment of Hemophilus Influenzal Meningitis. *J.A.M.A.*, 143:1405, 1950.
61. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion, and Distribution of Penicillin. *J. Clin. Investigation*, 22:425, 1943.
62. Ross, S., and Burke, F. G.: Pneumococcus Meningitis in Infants and Children. *J. Pediat.*, 29:737, 1946.
63. Ross, S., and others: Treatment of Meningitis Due to Hemophilus Influenzae: Use of Chloramphenicol and Sulfadiazine. *New England J. Med.*, 247:541, 1952.
64. Schoenbach, E., Spencer, H., and Monnier, J.: Treatment of Hemophilus Influenzae Meningitis with Aureomycin and Chloramphenicol. *Am. J. Med.*, 12: 263, 1952.
65. Schwartz, A. B.: Etiology of Pachymeningitis Hemorrhagica Interna in Infants. *Am. J. Dis. Child.*, 11:23, 1916.
66. Scott, J. R., and Walcher, D. N.: Chloramphenicol in the Treatment of Meningitis Due to Hemophilus Influenzae. *J. Pediat.*, 41:442, 1952.
67. Severy, W. L.: Meningitis, A Review of One Year's Cases from an Active Children's Hospital Service. *California Med.*, 82:436, 1955.
68. Shaw, E. B.: Conferences at Communicable Diseases Department, Children's Hospital, San Francisco, California. *J. Pediat.*, 40:376, 1952.

69. Smadel, J. E.: Chloramphenicol in the Treatment of Infectious Diseases. *Am. J. Med.*, 7:671, 1949.
70. Smiley, R. K., Cartwright, G. E., and Wintrobe, M. M.: Fatal Aplastic Anemia Following Chloramphenicol Administration. *J.A.M.A.*, 149:914, 1952.
71. Smith, E.: Purulent Meningitis in Infants and Children. *J. Pediat.*, 45:425, 1954.
72. Smith, E.: Salmonella Meningitis in Infancy. *Am. J. Dis. Child.*, 88:732, 1954.
73. Smith, M. H. D., Dormont, R. E., and Prather, G. W.: Subdural Effusion Complicating Bacterial Meningitis. *Pediatrics*, 7:34, 1951.
74. Smith, R. T.: Septicemia and Meningitis in a Newborn Infant. *J. Pediat.*, 47:740, 1955.
75. Spitz, E., Pollak, A., and Angrist, A.: Subdural Suppuration Originating in Purulent Leptomeningitis. *Arch. Neurol. & Psychiat.*, 53:144, 1945.
76. Sweet, L. K., Dowling, H. D., and Howell, M. J.: Acute Meningococcemia. *J. Pediat.*, 30:438, 1957.
77. Thomas, L., and Dingle, J. H.: Investigations of Meningococcal Infections. *J. Clin. Investigation*, 22:353, 1943.
78. Thomas, L., Smith, H. W., and Dingle, J. H.: Investigation of Meningococcal Infection. Immunological Aspects. *J. Clin. Investigation*, 22:361, 1943.
79. Turner, E. K.: Hemophilus Influenzae Meningitis in 40 Infants Treated with Sulfonamides, Type-Specific Anti-serum and Penicillin at the Children's Hospital, Melbourne. *M. J. Australia*, 2:745, 1948.
80. Waterhouse, R.: Case of Suprarenal Apoplexy. *Lancet*, 1:577, 1911.
81. Wheeler, D., and Amidon, E. L.: Waterhouse-Friderichsen Syndrome; Report of a Case with Recovery. *New England J. Med.*, 247:256, 1952.
82. Wilkes-Weiss, D. W., and Huntington, R. W., Jr.: Treatment of Influenzal Meningitis with Immune Serum. *J. Pediat.*, 9:462, 1936.
83. Wilson, L. E., Harris, M. S., Henstell, H. H., and Witherbee, O. O.: Aplastic Anemia Following Prolonged Administration of Chloramphenicol. *J.A.M.A.*, 149:231, 1952.
84. Wilson, L. E., and others: Aplastic Anemia Following Prolonged Administration of Chloramphenicol. *J.A.M.A.*, 149:231, 1952.
85. Winternitz, C.: Fatal Aplastic Anemia Following Chloramphenicol Therapy. *California Med.*, 77:335, 1952.
86. Wright, S. S., Purcell, E. M., Wilcox, C., Broderick, M. K., and Finland, M.: Antibiotic Combinations and Resistance to Antibiotics. *J. Lab. & Clin. Med.*, 43:877, 1953.

4614 Sunset Boulevard
Los Angeles 27, California

ANTIMICROBIAL THERAPY IN CARDIOVASCULAR INFECTIONS

BURTIS B. BREESE, M.D.

In this paper the discussion of antimicrobial treatment of diseases of the circulatory system in children will be limited to the prevention of rheumatic fever by control of beta streptococcal infections and the treatment of subacute bacterial endocarditis.

Other diseases which affect the circulatory system, such as diphtheria and viral or bacterial infections, are either best not treated by antimicrobial agents or are a complication of generalized infections whose treatment is discussed elsewhere in this symposium.

RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

Importance of Streptococcal Infection in Rheumatic Fever

Probably all initial attacks and recurrences of rheumatic fever are initiated by beta hemolytic streptococcal infections. The mechanism by which this occurs is unknown, but the mass of data confirming this hypothesis is overwhelming. Once the rheumatic process has begun, there is little that one can do to stop the effect of the disease process on the heart and heart valves, although the symptoms may be ameliorated by salicylic or hormone therapy.

It is therefore apparent that one must attack the etiologic agent—the hemolytic streptococcus—if one is to prevent rheumatic fever. Unfortunately there is no effective method of preventing streptococcal infection in the general population. However, Rammelkamp and his

From the Department of Pediatrics, University of Rochester School of Medicine and Dentistry, and the Strong Memorial Hospital, Rochester, New York.

associates showed, in a group of Air Force trainees, that adequate penicillin therapy of the streptococcal infection prevented rheumatic fever in the treated subjects, whereas in the untreated ones approximately 3 per cent acquired the disease.[8] Furthermore, they showed that the effectiveness of the preventive method could be roughly measured by its ability to eliminate the streptococcus from the host.[6]

The application of any method of therapy is dependent upon our knowledge of a disease and its proper diagnosis. We shall therefore digress here to discuss streptococcal infection in children.

Frequency. That streptococcal infections are exceedingly common in pediatric practice is made apparent by the fact that my associate, Dr. Frank A. Disney, and I have seen in the course of the last three or four years from 500 to 800 cases of bacteriologically proved streptococcal infection in children each year. Most of the cases occur in the age group of five through eight, but they may be observed at any age. In 80 per cent of our cases the primary diagnosis was streptococcal sore throat and in 13 per cent scarlet fever. Otitis media and cervical adenitis were the most common secondary infections.[4]

Diagnosis. It is the sore throat, therefore, with or without a rash that one must recognize. Sensitized as we are to the disease, our over-all "batting average" recognizing streptococcal infection on clinical grounds alone is about 750 (75 per cent).[3] In other words, we missed about one case in four!

The age of the patient was an important factor in our ability to diagnose properly. The younger the child, the more difficulty we encountered. For example, we were correct in our diagnosis 88 per cent of the time in children 12 years of age or older and in only 56 per cent of the time in children two or under. Rantz has emphasized this point and shown that the young child's infection is often difficult to diagnose.[11]

No single group of symptoms or signs was infallible. In general, a sore throat which "hurt to swallow" associated with fever of 101° F. or over, especially in the winter and spring months, was suggestive of streptococcal sore throat. If, in addition, the patient's throat was inflamed, and exudate was present, the diagnosis was very likely to be streptococcal disease. When cough, coryza or hoarseness is associated with a sore throat, this is strong evidence that the infection is not streptococcal in origin.

However, many younger patients did not present these symptoms or signs, especially if seen within 24 hours of onset, and laboratory aid, we feel, is most helpful. We have relied strongly on a simple white blood cell count. With streptococcal disease the count is rarely below 12,000 and often as high as 30,000. As our final diagnostic criterion we have used a culture of the throat.

We carry in our bags sterile swabs and rubber-stoppered test tubes containing a small amount of infusion broth. At the time of a house visit it is a simple matter to take a culture and place it in the tube, which will keep it well for at least 24 hours. On our return to the office these swabs are streaked on blood agar plates. By the next morning the plates are read. By using sheep blood agar, the typical beta hemolytic colonies are readily identified grossly.

Lastly, one might cite the therapeutic response as a diagnostic method. A streptococcal infection will almost invariably be vastly improved within 12 to 24 hours after treatment by almost any of the antibiotics, particularly penicillin. Failure to observe such a response is strong evidence against the streptococcus as the etiologic agent.

Treatment of Streptococcal Infection. Once having arrived at a diagnosis, the question of what treatment is most effective arises. Penicillin therapy is preferable. The drug should be given so that bactericidal amounts of the drug remain in the blood stream for at least a week, or preferably 10 days.

The "broad-spectrum" antibiotics, although of value in treatment, are definitely less effectual than penicillin. Since they are bacteriostatic, their use is associated with inferior ability to eliminate the organism from the throat permanently and with a high rate of clinical relapse.[4, 6] The sulfonamides are even less effectual as therapeutic agents in acute cases of streptococcal infection.

Bactericidal amounts of penicillin may be maintained for a week or 10 days by the use of either oral or intramuscular penicillin. At the time of this writing we prefer to use a single dose of 600,000 units of dibenzyl penicillin G intramuscularly. In a series of over 1000 children we have found the drug uniformly effective.[2, 4] Its action is prompt, the recurrence rate is low, and we have not observed any cases of rheumatic fever in our entire series. Furthermore, it is cheaper for the patient than any oral method and eliminates the uncertainty and difficulties of giving sick, frequently nauseated children oral medication. Although almost all children complain of pain at the site of injection which is at times severe, the general allergic reaction rate is under 2 per cent and no higher than with oral medication.

If oral medication is used, one has a wide latitude of choice. The ordinary buffered potassium penicillin G in divided dosage of 800,000 to one million units daily given for 10 days is effective and probably the least expensive oral medication. It should be given preferably on an empty stomach.

The dibenzyl penicillin G preparation when given orally is, because of its low solubility, extremely palatable. It is given in about the same dosage as noted earlier. The level of penicillin in the blood may be increased by the addition of a kidney-blocking substance, probenecid.

This material is commercially available combined with penicillin. Many other oral penicillin preparations are available in almost endless combinations and forms. The most recent preparation to come on the market is Penicillin V. It has the theoretic advantage of not being broken down by the acidity of the gastric juice. We have used it with success in well over 100 cases of streptococcal disease in children with a resulting "cure rate" of approximately 90 per cent.

It should be remembered that no matter what preparation is used, the drug must be continued for 10 days, not always an easy feat in a child. Penicillin lozenges are of little value therapeutically.

THE PREVENTION OF RHEUMATIC FEVER IN PATIENTS WITH PREVIOUS RHEUMATIC FEVER

Danger of Streptococcal Infections

Since, as a rule, it is the polycyclic attacks of rheumatic fever which are responsible for the great damage that the disease does to the heart, the prevention of recurrences should be our aim. Although the nonrheumatic person is faced with at most a 3 per cent chance of acquiring rheumatic fever after a streptococcal infection, the person who has previously had rheumatic fever may be faced with a 50 per cent risk of a recurrence. It is in this group that prophylaxis with drugs is most effective. Such patients, when the history of rheumatic fever seems definite or when unquestioned rheumatic heart disease exists, should be placed on continuous prophylaxis throughout the year, which should, we feel at present, be continued indefinitely.

Preventive Measures

Much experience is now collected on the effectiveness of such prophylactic measures. One has available three methods: (1) the daily oral use of one of the sulfonamides (we use sulfadiazine) in a dose of 0.5 to 1.0 gm. daily; (2) the daily oral use of some penicillin preparation (such as potassium penicillin G or dibenzyl penicillin G in a dosage of 200,000 units daily; (3) the monthly intramuscular injection of dibenzyl penicillin G in a dosage of 1,200,000 units as suggested by Stollerman.[12] All three methods are effective, and each has its advantage and disadvantages.

The sulfonamides are the least expensive, but have a somewhat higher reaction rate than penicillin. The dosage is 0.5 to 1.0 gm. daily, the smaller dose being used in children.

The toxic reactions observed usually occur within the first eight weeks. Morbilliform skin eruptions are most common and usually not

serious. Such rashes generally disappear even if the drug is continued. Scarlatiniform rashes are generally more serious. They are apt to occur much more promptly than morbilliform eruption and are often associated with a sore throat so similar to that found in scarlet fever that one has great difficulty in separating the two diseases. Redness and itching of the eyes strongly suggest a drug eruption. Urticaria also occasionally occurs with the use of the sulfonamides. If either of the last two reactions occurs, the drug should be stopped.

On rare occasions agranulocytosis may occur during the first eight weeks of prophylaxis. For this reason weekly white blood cell counts are advised during this period. If the count falls below 4000 and polynuclear neutrophils below 35 per cent, the drug should be discontinued.[7]

Penicillin orally is more expensive than the sulfonamides, but is bactericidal against the hemolytic streptococcus. Rarely it gives rise to toxic reactions of allergic nature such as urticaria, angioneurotic edema, and serum sickness-like responses which must be distinguished from rheumatic fever.

The injection of benzathine penicillin G may be followed by the same type of reaction as from oral penicillin and, in addition, soreness at the site of injection.

SUBACUTE BACTERIAL ENDOCARDITIS

Frequency

The recent advances in antimicrobial therapy have reduced the over-all mortality from this disease from one of almost 100 per cent to somewhere around 30 to 40 per cent. Since the disease is generally engrafted upon heart valves damaged by rheumatic fever or congenital abnormalities of the heart, the reduction in the incidence of the former disease is reflected in a decrease in the number of cases of bacterial endocarditis in children. Never a common disease, it is now rare indeed in the pediatric population. In recent years, however, operative procedures for the correction of congenital heart disease such as the Blalock-Taussig operation for the tetralogy of Fallot have produced a new group of patients who now survive in whom the disease may appear at the operative site.

In contrast to the treatment and diagnosis of acute beta hemolytic streptococcal infection, which can be carried on quickly and readily in the home with a minimum of laboratory aids, subacute bacterial endocarditis is a disease which needs for diagnosis and therapy facilities available only in the modern hospital.

Diagnosis

In a child with congenital or rheumatic heart disease the occurrence of persistent fever, often not high, should suggest the possibility of subacute bacterial endocarditis. In 181 patients with congenital heart disease who were over the age of two at the time of death reported by Gelfman and Levine,[9] 16.5 per cent had subacute bacterial endocarditis. In Bland and Jones'[1] series of rheumatic fever patients followed up for 20 years about 5 per cent acquired the disease in about 10 to 15 years. Even in the absence of known cardiac disease persistent unexplained fever may be caused by this disease. None of the general symptoms such as malaise, anorexia and pallor is diagnostic of the disease. Heart murmurs are generally present and may change with the progression of the disease. Embolic phenomena such as petechiae of the skin, mucous membrane and fundi, nodules of the tip of fingers and flame or splinter hemorrhage under the nails are characteristic but often lacking. Embolic phenomena of the nervous system and abdominal viscera such as spleen and kidneys may also be observed. The spleen is enlarged in about 50 per cent of cases.

Diagnosis is confirmed by finding of repeated positive blood cultures. This is frequently a difficult task, and some cases, despite repeated attempts by competent laboratories, run the full course of the disease without the organism being found.

Bacteriology

Ninety per cent of the organisms responsible for subacute bacterial endocarditis are the streptococci, which are common normal inhabitants of the upper respiratory passages, and those found most commonly in the gastrointestinal tract, or enterococci. The former, or viridans, group is generally sensitive to penicillin in amounts under 1.5 units per milliliter. The latter group, or enterococci, on the other hand, is almost always resistant to penicillin in amounts up to 1.5 units per milliliter, but usually sensitive to quantities under 10 units per milliliter. The enterococci are responsible for approximately 20 per cent of these streptococcal infections.

Treatment

Both the viridans group and the enterococci are sensitive in vitro to "broad-spectrum" antibiotics and relatively insensitive to dihydrostreptomycin and streptomycin. However, experience has shown that the former group of drugs are relatively ineffective in curing bacterial endocarditis, but that streptomycin has a marked synergistic effect with penicillin that is very effective in curing the disease.

Accordingly, penicillin and streptomycin are used together in treating both the penicillin-sensitive and relatively penicillin-resistant strains of streptococci found in subacute bacterial endocarditis. The duration and the amount of therapy are, however, much greater in the cases caused by penicillin-resistant strains. The addition of the kidney-blocking substance probenecid may help materially in increasing the blood levels obtained with penicillin.

Dosage. In Sensitive Organism. Six hundred thousand units daily of procaine crystalline penicillin G are given plus 0.6 gm. of dihydrostreptomycin every 12 hours for a period of three weeks.

In Resistant Organisms. Twelve million units of crystalline penicillin G are given by intravenous drip through a polyethylene tube. Bunn[5] prefers to dissolve the penicillin in 250 to 500 cc. of saline solution and give as a slow intramuscular or subcutaneous infusion.

In addition, a combination of 0.5 gm. of streptomycin and 0.5 gm. of dihydrostreptomycin twice daily has been reported by Geraci and Martin[10] as efficacious and relatively nontoxic. Besides these two drugs, 0.5 gm. of probenecid given four times daily elevates the blood level of penicillin appreciably. This combination of therapy when used for a six weeks' period is generally effective in curing the disease.

Other Problems in Therapy. Although in most cases it is now possible to sterilize the blood stream, deaths will still continue to occur. Today these stem largely from embolic phenomena, rupture of valve leaflets and intractable cardiac failure.

Prevention

Since transient bacteremia following dental work, tonsillectomy and surgical procedures in the genitourinary tract may be responsible for cases of subacute bacterial endocarditis in patients with rheumatic or congenital heart disease, penicillin prophylaxis is advisable at the time of such procedures.

For prophylaxis the Committee on the Prevention of Rheumatic Fever and Bacterial Endocarditis of the American Heart Association recommend as the most effective measure the use of 600,000 units of aqueous penicillin and 600,000 units of procaine penicillin in oil containing 2 per cent aluminum monostearate 30 minutes before the operative procedure.[7]

REFERENCES

1. Bland, E. F., and Jones, T. D.: Rheumatic Fever and Rheumatic Heart Disease: A Twenty Year Report on 1000 Patients Followed since Childhood. *Circulation*, 4:836, 1951.

2. Breese, B. B.: Treatment of Beta Hemolytic Streptococcic Infections in the Home; Relative Value of Available Methods. *J.A.M.A.*, 152:10, 1953.
3. Breese, B. B., and Disney, F. A.: The Accuracy of Diagnosis of Beta Streptococcal Infection on Clinical Grounds. *J. Pediat.*, 44:670, 1954.
4. Breese, B. B., and Disney, F. A.: The Successful Treatment of Beta Hemolytic Streptococcal Infections in Children with a Single Injection of Repository Penicillin. *Pediatrics*, 15:516, 1955.
5. Brenn, P. A., and Cook, E. T.: Treatment of Subacute Bacterial Endocarditis. *Ann. Int. Med.*, 41:487, 1954.
6. Chamovitz, R., Calanzaro, F. J., Stetson, C. A., and Rammelkamp, C. H.: Prevention of Rheumatic Fever by Treatment of Previous Streptococcal Infections. *New England J. Med.*, 251:466, 1954.
7. Committee on Prevention of Rheumatic Fever and Bacterial Endocarditis, American Heart Association. *Circulation*, 2:317, 1955.
8. Denny, F. U. V., Wannemaker, L. W., Brink, W. R., Rammelkamp, C. H., and Custer, E. A.: An Effective Method for the Prevention of Rheumatic Fever after the Development of a Streptococcal Infection. *J. Lab. & Clin. Med.*, 34:1596, 1949.
9. Gelfman, R., and Levine, S. A.: The Incidence of Acute and Subacute Bacterial Endocarditis in Congenital Heart Disease. *Am. J.M. Sc.*, 204:324, 1942.
10. Geraci, J. E., and Martin, W. J.: Antibiotic Therapy of Bacterial Endocarditis—Subacute Enterococcal Endocarditis. *Circulation*, 10:173, 1954.
11. Rantz, L. W., Maroney, M., and DiCaprio, J. M.: Infection and Reinfection by Hemolytic Streptococci in Early Childhood, in *Rheumatic Fever—A Symposium*. Minneapolis, University of Minnesota Press, 1952, p. 90.
12. Stollerman, G. H., and Rusoff, J. H.: Prophylaxis against Group A Streptococcal Infection in Rheumatic Fever Patients: Use of New Repository Penicillin Preparation. *J.A.M.A.*, 150:1571, 1952.

2333 Elmwood Avenue
Rochester 18, New York

ANTIMICROBIAL THERAPY IN GASTROINTESTINAL TRACT INFECTIONS

RALPH H. KUNSTADTER, M.D.

ROBERT M. KOHLENBRENER, M.D.

Antimicrobial therapy has made necessary a careful diagnostic approach to gastrointestinal infections. There is usually an antimicrobial drug of choice for any specific infection. Rational use of the best available drug should be based on etiologic diagnosis when possible.

BACTERIAL INFECTIONS

Infections of the gastrointestinal tract may be relatively mild, and respond to simple diet restriction and symptomatic therapy. Although these mild cases may be due to infection by recognized pathogens, prompt response to simple management usually makes it unnecessary to do bacteriologic studies. Special situations such as the appearance of even slight diarrhea in a newborn nursery, premature nursery or infant nursing home should stimulate efforts to make a definitive etiologic diagnosis, so that appropriate prophylactic measures and antimicrobial therapy can be used to prevent a serious epidemic. Except for these special situations, the application of diagnostic laboratory procedures is practically limited to the more severe cases of diarrhea or to the recurrent or protracted diarrheas that result in a general failure to thrive.

A variety of antimicrobial agents are available for effective therapy of gastrointestinal and other infections. The rational use of these agents demands that the drug be chosen with the probable or proved sensi-

From the Sarah Morris Hospital for Children, Michael Reese Hospital, Chicago.

tivity of a definite pathogenic organism in mind. Diarrhea and vomiting are only symptoms that reflect conditions of irritation and inflammation of the gastrointestinal tract. The severity of these symptoms is in direct proportion to the toxic effect of the etiologic agent, but the symptoms themselves are not helpful in determining the etiology in any particular case. Problem cases, whether acute or chronic, should be approached with emphasis on determining etiology rather than with attempts to cover all possible pathogens by the administration of one of the broad-spectrum antibiotics.

Diarrhea. Diarrhea is primarily a problem of infancy, with the peak incidence in formula-fed infants between the first and fourth months. In our experience the disease is no longer of epidemic proportion during the hot summer months, but there are peaks of incidence in July, November and December. May and June are the months when the disease is least likely to occur.

The infant stricken with diarrhea has usually been in good health. The median incubation period, if there is a contact history, is seven days, but is often shorter. Usually the first indication of illness is a sudden change of stool consistency from formed to semiliquid. Vomiting may or may not be present and may be the only sign at the onset. Stool frequency rapidly accelerates, and, in the severe case, the infant expels 10 to 15 yellow-green liquid stools a day. The onset of the disease often is associated with irritability, but this gives way to lethargy as dehydration and toxicity increase. Anorexia is usual, though some infants will take fluids throughout the disease. When brought to the hospital after several days of the disease, the infant presents a picture of cachexia. His color is ashen. The fontanel and eyeballs are sunken. Skin turgor is poor, and the mucous membranes are dry. Abdominal distention may be prominent. Blood chemistry studies reveal a marked metabolic acidosis. The urine is scanty and contains albumin, casts and a few white cells, but no acetone if the infant is younger than six months.[34] The white blood cell count is 10,000 to 20,000 with increased neutrophils and a shift to the left.

The syndrome just described can be caused by any of the enteric bacterial pathogens. Commonly, in our experience and that of others,[50, 84] a pathogen may not be isolated despite complete bacteriologic studies. Parenteral infection, whether apparent or inapparent, has often been implicated as a cause of infantile diarrhea. Wolfish[84] reported that 40 per cent of his series of 518 cases of gastroenteritis had evidence of parenteral infection. He admits, however, that the relation between parenteral infection and gastroenteritis is most indefinite. A viral etiology in some of the unexplained cases has been postulated, and experimental evidence supporting this theory has been reported by Light and Hodes.[52]

Salmonella and Shigella

The more than 150 Salmonella strains have been classified into five main groups on the basis of antigenic differences. Specific identification of the strain is of epidemiologic importance. Certain strains cause characteristic types of infections. *Salmonella typhosa* produces the enteric fever syndrome, typhoid fever. *Salmonella typhosa* will live only in man; most of the other Salmonellae have reservoirs in animals. *Salmonella paratyphi* and *Salmonella schottmuelleri* cause a milder enteric fever, paratyphoid fever. *Salmonella typhimurium* causes acute gastroenteritis. *Salmonella choleraesuis* produces septicemia and foci of infection. These associations are general and not definite, for any of the Salmonellae may manifest enteric fever, gastroenteritis or septicemia with foci.

In 1954, 7.4 per cent of the 203 cases of enteritis among patients admitted to the pediatric division of Michael Reese Hospital were due to Salmonella. Only three strains, *Salmonella montevideo, Salmonella typhimurium* and *Salmonella newport,* accounted for two thirds of the cases. In this group only one death occurred, a premature infant with anomalies. Saphra[71] has reported a mortality rate of 5.3 per cent in a series of 3279 cases of Salmonella infections.

The common Shigella strains causing dysentery in the United States are Flexner and Sonnei. Only 2.5 per cent of our 203 enteritis admissions proved to be due to Shigella. Both Flexner and Sonnei strains were represented. This low incidence is in marked contrast to the 28 per cent reported by Levinson and Raycraft[50] also from Chicago. Kaliski and Geppert[40] reported a 12.7 per cent incidence from Texas. Shigella infection is uncommon in young infants and has not been reported as a cause of epidemic diarrhea of the newborn. Levinson and Raycraft[50] found 71 cases of Shigella infection in children over one year to only seven cases in infants under one year in their series of 300.

The presence of blood in diarrhea stools is excellent presumptive evidence for a Salmonella or Shigella etiology. However, absence of bloody stools does not exclude these organisms. Feig[24] described an epidemic of Shigella enteritis and found that 28 per cent of the children under five years and 40 per cent of those between six and 15 years had bloody stools.

Pathogenic Escherichia Coli

The first substantial evidence implicating an *Escherichia coli* serotype as a cause of infantile diarrhea was reported by Bray[8] in 1945. Kauffman[41] designated Bray's serotype *E. coli* 0111:B4 in his classifica-

tion based on antigenic differences. The list of all *E. coli* serotypes now numbers almost 130.

Since 1945, six serotypes have been associated with outbreaks of infantile diarrhea. They are 026:B6,[63] 055:B5,[76] 073,[61] 086:B7,[7] 0111:B4[72] and 0127:B8.[13] Epidemics due to these organisms have been limited to premature and newborn nurseries. In former years the nursery calamity known as epidemic diarrhea of the newborn was probably due to unidentified *E. coli* serotypes in many instances.

Sporadic diarrhea any time during infancy may be due to infection with pathogenic *E. coli*. Our experience has not included an epidemic due to *E. coli*, but we have seen several cases of sporadic infantile diarrhea due to serotype 0111:B4. Between September, 1954, and September, 1955, ten infants admitted to our hospital because of diarrhea were found to have this serotype in their stools. The ages of these infants ranged from two to 12 months. Despite the extreme contagion that is characteristic when pathogenic *E. coli* invades a newborn nursery, we have not seen the infection spread from a known *E. coli* diarrhea case to another infant not involved. Cubicle and gown isolation technique are observed on our infant wards, but the same nurses take care of infected and clean cases. Asymptomatic adult carriers have been implicated in at least one epidemic.[82] Airborne spread from the upper respiratory tract has also been postulated.[60]

Diarrhea due to pathogenic *E. coli* is characterized by spontaneous remissions and relapses. In those outbreaks that occurred prior to the use of effective antibiotics, many infants died during relapses. The 1947 epidemic in Aberdeen, Scotland, was notable for a mortality rate of 50.6 per cent of 207 infants found to have serotype 0111:B4 in their stools.[28] During the acute stage of the enteritis the pathogenic serotype appears in almost pure culture. The relative proportion of the serotype to other coliform organisms decreases rapidly as the infant's condition improves. .

Pathogenic E. coli *serotypes have the same cultural characteristics as nonpathogenic serotypes.* Stool culture studies that include only media designed to inhibit *E. coli* are obviously inadequate. Culture on media such as blood agar or MacConkey's agar must be included. Even when *E. coli* growth is encouraged, the recognition of a pathogenic strain depends on serologic typing. Definitive typing is done in only a few large laboratories, but experienced bacteriologic technicians can sometimes spot suspicious colonies by subtle differences in appearance. One characteristic that is helpful is that pathogenic *E. coli* cultures may have a musty semen-like odor.[8] It has been observed that the patients with *E. coli* diarrhea may have a similar pungent musty odor that is not associated with diarrhea due to other causes.[13]

Paracolon, Pseudomonas and Proteus

Good evidence exists that paracolon bacilli may be enteric pathogens. One of us (R.H.K.) has seen three infants who died of diarrhea and sepsis due to paracolon.[48] These three fatalities were from the same foster home where five of seven infants had diarrhea. In June, 1955, a seven year old girl was admitted to our hospital with fulminating bloody diarrhea, vomiting and fever. She died three hours after admission, and autopsy revealed an acute gastroenteritis with marked lymphoid hyperplasia of Peyer's patches, mesenteric nodes and the spleen. Only paracolon was cultured from the intestinal contents and biliary tract. A typhoid-like infection in in adult due to paracolon was reported from Michael Reese Hospital a few years ago.[6] Certain types of paracolon bacteria such as biotype 32011 (aerobacter)[80] and members of the Arizona group[21, 58] have been particularly implicated as pathogens.

Pseudomonas aeruginosa produces enteritis with diarrhea in both children and adults.[78] Hunter and Ensign[37] reported a serious epidemic of diarrhea of the newborn due to this organism. In recent years the role of *Ps. aeruginosa* as an enteric pathogen has been confused by the marked increase in incidence of this organism in the intestinal tracts of patients who received broad-spectrum antibiotics for any reason. When the normal intestinal flora is suppressed by antibiotics, resistant *Ps. aeruginosa* often becomes predominant. This is also true of *Proteus* strains. Nevertheless, early in 1954 the microbiology laboratory of Michael Reese Hospital stopped recording *Ps. aeruginosa* cultured from stools as a pathogen, because the incidence of this organism in these cultures had become exceedingly common. Recently a report from Israel[75] differentiated normal intestinal flora from the transient flora that was found frequently in malnourished infants with diarrhea. *Pseudomonas aeruginosa* and *Proteus* strains were components of the transient flora.

Proteus morganii was originally isolated from the stools of infants with diarrhea.[57] It has since been implicated in a number of outbreaks of infantile diarrhea,[59] but its etiologic significance is still not well established. The position of *Proteus mirabilis* as an enteric pathogen is even less secure than that of *P. morganii*.[10, 56] The parallel increase of incidence of *Proteus* strains and *Ps. aeruginosa* since the advent of antibiotics has already been mentioned.

Since the status of *Ps. aeruginosa* and the *Proteus* strains as enteric pathogens is ill defined at present, the clinician must decide the importance of these organisms in each individual case. Our policy has been to treat them with an effective antibiotic when the patient's diarrhea does not respond to nonspecific therapy.

Staphylococcus

Diarrhea due to coagulase-positive *Staphylococcus aureus* also is a phenomenon that has assumed importance in the antibiotic era. It is important because it tends to be severe and often fatal. Garland[27] thoroughly reviewed the general problem and also defined the relation of staphylococcal enteritis to pseudomembranous enterocolitis. Finland's group[26] has since observed that the incidence of staphylococcal diarrhea depends on both the type of antibiotic and the dosage that is used: incidence was higher with Terracycin than with Aureomycin and decreased proportionately when the dosage of either was lowered. The role of tetracycline as a cause of this complication has not yet been defined.

Staphylococcus enteritis has had much less attention in the pediatric age group than in the adults. Hay and McKenzie[32] described complications of Terramycin therapy that included a fatal case of fulminating staphylococcus enteritis in a six year old girl. Cramer and Rossi[15] reported five fatal cases of diarrhea in children secondary to Terramycin and Aureomycin therapy. Two of their cases had pseudomembranous enterocolitis that was credited to *Staph. aureus*. Nyhus and Burke[62] described a nine year old boy with staphylococcus enteritis and pseudomembranous enterocolitis who recovered.

Therapy

The infant with diarrhea often has serious water and electrolyte imbalance which requires prompt correction by calculated intravenous fluid administration. Fluid therapy is of primary importance during the early phase of treatment, and often fluid therapy and diet adjustment alone are all that is needed. Discussions of fluid and electrolyte therapy have appeared in recent *Pediatric Clinics*.[31, 65, 67]

Over-all care of the patient integrates antibiotic, fluid and electrolyte, diet and adjuvant therapy. Rational antibiotic therapy must be directed toward the elimination of a specific pathogen. Determination of such a pathogen depends on thorough bacteriologic culture studies of the intestinal flora, the nose and throat flora, and the blood. Serologic studies may also be necessary. These studies should be included in the initial work-up of any serious case of diarrhea. It is unfortunate that a lapse of one or more days must intervene between the time the cultures are set up and the time preliminary or final results are available. In some cases of staphylococcus enteritis an immediate indication of the etiologic organism can be gained by finding numerous gram-positive cocci in direct smears of mucus from the stool. Such an immediate report is unusual, and most often the choice of initial therapy must be an agent that will provide the best broad-spectrum coverage for the

wide range of enteric pathogens. When the culture report and subsequent sensitivity studies are available, it is possible that the initial antibiotic will be changed for one that is more effective.

Chloramphenicol and neomycin both have broad spectrums that include most of the enteric pathogens.[42] Either of these antibiotics is a good choice for initial therapy before culture and sensitivity results are known. These drugs are more effective against pathogenic staphylococci and *E. coli* than are the tetracyclines. Chloramphenicol is absorbed from the intestinal tract, and, therefore, will suppress systemic Salmonella infections.[49] Neomycin is not appreciably absorbed and acts only on bacteria within the intestinal lumen. When bloody diarrhea suggests that Salmonella may be the etiologic organism, chloramphenicol is the drug of choice. Also, chloramphenicol can be given intravenously or intramuscularly in cases in which vomiting precludes oral administration. Neomycin can be given by the intramuscular route, but it is very toxic. The oral dosage that we have found effective for both chloramphenicol and neomycin is 50 mg. per pound per day divided into four doses and given every six hours. The intramuscular dosage of chloramphenicol is 50 mg. per pound per day divided into two doses, and the intravenous dosage is 25 mg. per pound per day divided into two doses at 12 hour intervals.

After a pathogen has been isolated sensitivity studies will provide further information about the antibiotic of choice. In many cases it will be found that the initial drug chosen is effective in vitro and a change will not be necessary. If the clinical response of the patient has been satisfactory, the antibiotic should not be changed even though the sensitivity studies in vitro indicate that it is not the most effective drug. An exception to this statement must be made if the pathogen is a Shigella strain. Infection due to Shigella may respond to any of the broad-spectrum antibiotics or sulfonamides, but relapses are not uncommon. Oral polymyxin is the most effective antibiotic for Shigella infections.[51] The oral dosage of polymyxin is 5 to 10 mg. per pound per day divided into four doses given every six hours.[42]

Pathogenic *E. coli* serotypes are best treated with neomycin or chloramphenicol. Other antibiotics have been used with some success, but resistant strains develop more rapidly than with the two recommended.[77, 83] A particular *E. coli* serotype may be resistant to either chloramphenicol[83] or neomycin,* but resistance to both drugs has not been reported.

In our experience, paracolon infections are best treated with chloramphenicol or neomycin. If systemic involvement is present, either of these drugs may be given parenterally.

* M. Robbins: Personal communication.

Pseudomonas aeruginosa responds to both polymyxin and neomycin.[42] Polymyxin is the drug of choice.[38, 39]

Proteus infections are best treated with neomycin.[42]

Staphylococci are most sensitive to chloramphenicol, erythromycin and neomycin. Sensitivity studies are important because of the high percentage of resistant strains. Oral erythromycin dosage is 25 mg. per pound per day in divided doses every six hours, and the intravenous dosage is 16 mg. per pound per day.[42]

PROTOZOAN INFECTION

Amebiasis

Since World War II there has been an increase in the reported incidence of amebiasis in the United States, in both children and adults, probably a result of numerous untreated carriers who had been members of the Armed Forces and served in endemic areas. The incidence varies geographically from approximately 0.8 per cent to 20 per cent throughout the world in children of all ages.[14, 19, 23, 55, 73] From Michael Reese Hospital, Howell and Knoll[36] reported an incidence of 3.18 per cent in children eight months to 13 years of age, and recently Goldenberg and his associates[29] reported an incidence of 9.2 per cent among 872 cases of diarrhea in infants and children observed at the Cook County Hospital in Chicago. In all probability the incidence in children would be higher if careful studies of stools by trained observers were performed on all patients with chronic or recurrent diarrhea and those individuals with ill defined gastrointestinal symptoms for which no explanation can be found.

In children the disease may manifest itself as an acute and frequently bloody diarrhea,[81] diarrhea alternating with constipation, recurrent diarrhea, or a bizarre and equivocal symptom complex.[53] Upon analysis of the clinical history and course of the disease in infants under one year of age, Goldenberg and associates[29] divided their patients into four groups: (1) infants who had an occasional loose stool with alternate normal bowel movements or obstipation, occasionally mucus in the stools; (2) infants who entered the hospital acutely ill, toxic, with dehydration and acidosis, and profuse, almost continuous watery stools with many showing marked pallor; (3) infants who had intermittent fever unexplained by physical findings or laboratory studies, diarrhea or obstipation, and slight enlargement of the liver with normal liver function tests; and (4) infants who presented the clinical picture of the celiac syndrome with marked abdominal distention and foul flatus. They appeared chronically ill, were not gaining weight and were poorly developed. The stools were bulky, large and light colored. Diarrhea was variable. Laboratory tests for celiac disease and fibrocystic disease

of the pancreas were negative. Some in this latter group resemble the picture described by Loeber and D'Antoni[53] in older children with bizarre symptoms which they believe presented patterns so variable as to defy orderly correlations, but concluded that "1. alterations in accustomed personality, appetite, and bowel habits were invariably present, 2. a peculiar though seemingly characteristic 'fading suntan' complexion together with a slightly enlarged and tender liver constituted the only distinctive physical signs common enough to be noteworthy, 3. complaints and abnormal physical signs subsided promptly with appropriate therapy."

The enlarged and tender liver that is frequently present in the chronic cases must not be confused with amebic hepatitis or abscess of the liver. Both are uncommon in childhood amebiasis, and neither responds to enteral antiamebic therapy, whereas the former subsides rapidly under treatment. With respect to asymptomatic amebiasis and the "carrier state," we agree with D'Antoni's statement that amebic carrier is a term of the past, and cysts and trophozoites in the stool mean actual tissue invasion, and all patients with intestinal parasitic infection should be treated.[18]

The diagnosis in suspected cases rests upon the demonstration of the trophozoites or cysts of *Entamoeba histolytica* in the feces or tissues. Several consecutive fresh stools may be necessary. In view of the fact that not more than 20 per cent of all cases can be identified by examining normally passed stools, in the absence of diarrhea, a saline purgative should be given. If fresh and satisfactory stool specimens cannot be obtained, proctoscopy is indicated. By means of proctoscopy not only can specimens be taken directly from the bowel, but also one has the opportunity of visualizing pathologic changes. Furthermore, proctoscopy is valuable in determining the results of treatment. Smears of the stool or material obtained from the bowel wall during proctoscopy are examined microscopically for trophozoites and cysts as soon as possible after mixing with physiologic saline solution and D'Antoni's iodine preparation.[17] Hematoxylin-stained smears may increase the number of positive results.[29]

The perfect amebicide is lacking, and the cure of amebiasis is often difficult. Because of low toxicity, nonabsorbed iodine preparations are the drugs of choice for children. Diodoquin has been the most popular and is given in full adult doses of three tablets (3.2 grains each) three times daily for 20 days to children weighing over 30 pounds.[18] Recently Goldenberg and associates[29] reported good results using iodinized bacitracin (10,000 units of bacitracin with 12.5 per cent iodine per tablet). Infants under 7 kilograms were given 10,000 units per day for 14 days; those over 7 kilograms 20,000 units per day for 14 days. As their children were all under one year of age, larger doses would have

to be given to older children. Relapses and resistant cases were treated with one or more of the following drugs: emetine hydrochloride, Milibis, Vioform, Aralen or a second course of bacitracin or Diodoquin. In spite of the possible dangers of arsenic poisoning, De Silva[19] used emetine parenterally and carbarsone enterally in 40 infants under two years of age. No toxicity occurred, and satisfactory results were obtained in 80 per cent of the cases, half of which were of the acute type and half the chronic and relapsing variety. Because reinfection by other members of the family is not uncommon, these contacts must be carefully examined and treated if positive. We have found that in the dysenteric patients a one to two week course of Sulfasuxidine or Sulfathalidine may be of value, since secondary bacterial infection is often present in these patients. Recently Fumagillin and Terramycin were found to be effective in the treatment of acute amebic dysentery.* Fumagillin (Fumadil) is recommended as the antibiotic of choice—10 to 20 mg. three times a day for 10 days.†

MYCOTIC INFECTIONS

Of the various systemic mycotic infections that occur in man, only three that involve the gastrointestinal tract justify description in this presentation. These are actinomycosis, histoplasmosis and candidiasis. Whether or not fungus infections may originate in the gastrointestinal tract is debatable. However, the fact that the symptoms associated with certain infections may be predominantly gastrointestinal cannot be disputed.

Actinomycosis

There is evidence that actinomycosis due to *Actinomyces bovis* occurs in an intestinal form as a result of invasion of the intestinal wall by organisms swallowed in the saliva. *Actinomyces bovis* is a frequent inhabitant leading a saprophytic existence in the oral cavity, respiratory tract and the gastrointestinal tract. There are some who believe that the organisms can penetrate the normal intact mucous membrane and produce infection. However, most writers believe, on the basis of clinical evidence, that only when the normal barrier of the intact mucosa has been destroyed by a previous infection or trauma can the organisms penetrate into adjacent tissue and become pathogenic.[68] The disease involves predominantly the ileocecal region, and the symptoms and physical findings suggest acute or subacute appendicitis. With pro-

* R. W. Sappenfield and others: Therapeutic Aspects of a Water-Borne Outbreak of Amebiasis in South Bend, Ind. *J.A.M.A.*, 159:1009, 1955.

† C. H. Brown, W. F. Gebhart and A. Reich: Intestinal Amebiasis. *J.A.M.A.*, 160:360, 1956.

gression, gangrene and perforation may result, or an irregular mass often develops. Progression is characterized by loss of weight, chills and fever, night sweats, abdominal cramps and vomiting. Sinuses may develop in the abdominal wall. Extension to the liver, genitourinary tract and vertebral bodies may occur.[12, 68] The diagnosis is rarely made without exploratory laparotomy unless draining sinuses are present. The prognosis for life is believed to be better in the intestinal than in the pulmonary form; nevertheless the disease is chronic, and invalidism is not uncommon. In addition to adequate surgery, the use of penicillin, the tetracyclines and sulfadiazine individually and in combinations may be helpful.

Histoplasmosis

Progressive histoplasmosis in children may have its portal of entry in the gastrointestinal tract. This explains the local ulcerations and common findings of mesenteric adenitis, hepatomegaly and splenomegaly. The onset in children is usually insidious with fever, diarrhea or other gastrointestinal symptoms, loss of weight, and enlargement of the liver and spleen. Anemia and leukopenia develop. There is generalized lymphadenopathy which is not prominent. With generalized dissemination the lungs, pleura and bone marrow also become involved. The duration of the disease is a few weeks to several months, shortest in young infants. Fortunately, less than one per cent of primary infections develop into the progressive and fatal form of the disease,[12] and usually the disease is benign.[64, 69] A benign and localized intestinal form is characterized by lesions that tend to heal, remain stationary, or are only slowly progressive.[74] Ulcerative enteritis has been reported.[33] Shull[74] suggests sigmoidoscopy in every patient suspected of having histoplasmosis of the intestinal tract, and, whenever possible, utilizing biopsy and direct smears with routine stain and culture of material from the lesion and from stool specimens as well. With dissemination the diagnosis is made by recovery of *Histoplasma capsulatum* from the blood, bone marrow, lymph nodes or tissue removed at biopsy, by culture and, if necessary, animal inoculation. The skin test and complement-fixation test may be helpful. As far as treatment is concerned, none is required in the benign forms. In progressive histoplasmosis the administration of ethyl vanillate as advocated by Christie and his associates may be of value.[11]

Candidiasis (Moniliasis)

Candida albicans often exists benignly in the oral cavity, respiratory tract and gastrointestinal tract, and invasion and infection by this

organism probably occur only under conditions of altered normal flora, lowered body resistance or a breakdown of the normal barrier of the mucous membane by infection or trauma. Extension of oral thrush into the esophagus and intestinal tract occurs more frequently than is reported. With extension into the esophagus there is refusal to feed or swallow, regurgitation and postprandial vomiting, often with blood. Death may occur from aspiration pneumonia or hematogenous dissemination.[85] Intestinal thrush rarely has been observed in infants and children.[4, 85] It probably occurs only in debilitated persons on swallowing saliva carrying the fungus from the mouth or esophagus. Recovery may occur spontaneously, or swallowing of saliva carrying gentian violet or some other therapeutic agent used locally in oral thrush may have a favorable therapeutic effect in the bowel.

Recent concern over intestinal candidiasis has arisen from the increased incidence of *Candida albicans* in the feces of patients who have received prolonged therapy with penicillin and/or the wide-spectrum antibiotics. Under such circumstances *Candida albicans* may become pathogenic and invade the intestinal tract. Although there is no proof that intestinal candidiasis is a clinical entity, we have seen cases of chronic diarrhea associated with heavy growth of *Candida albicans* in the stools associated with antibiotic therapy. In some of these cases no improvement followed antibiotic withdrawal, and only after the use of antifungal agents did clinical improvement result.* Usually discontinuation of antibiotics will result in spontaneous recovery from diarrhea and a decrease and eventual disappearance of these organisms from the stools. In resistant cases the administration of Mycostatin,† 100,000 to 500,000 units three times daily for five to 10 days, is indicated (each tablet contains 500,000 units; powder dissolved in water may be used for smaller doses). In our experience Mycostatin used topically in the mouth for thrush, and enterally for intestinal candidiasis, has proved superior to gentian violet topically or enterally.

"INFECTIONS" OF QUESTIONABLE ETIOLOGY

Under this heading are included pseudomembranous enterocolitis, regional enteritis and chronic ulcerative colitis. Although the etiology of these clinical entities is not clearly understood, they present clinical evidence of acute or chronic infection and pathologically show various stages of inflammation consistent with infection.

Pseudomembranous Enterocolitis

A review of our autopsy material over the past five years failed to disclose a single case of pseudomembranous enterocolitis in infancy or childhood, and yet Beatty and Hawes recently described 10 autopsied

* R. H. Kunstadter: Unpublished data on clinical trials with Mycostatin.

† Mycostatin (fungicidin, nystatin), E. R. Squibb and Sons.

cases in infants over a twelve year period from 1942 to 1954 at the Children's Hospital in Denver.[3]

Pseudomembrane formation is produced in the gastrointestinal tract by specific dysenteries, heavy metals and uremia. There are those cases for which no consistent etiologic agent has been demonstrated, but certain possible etiologic factors and associated conditions are recorded frequently, suggesting more than a casual relationship. These conditions are staphylococcus enteritis,[27] previous antibiotic therapy for various infections,[9, 22] surgical operations involving the gastrointestinal tract[20] and intestinal obstruction.[47] In the cases of Beatty and Hawes neither previous antibiotic therapy nor staphylococcus infection was considered important. It is significant that intestinal obstruction was present in 50 per cent of their patients and had occurred prior to evidence of enterocolitis. Furthermore, in no case were lesions noted distal to the obstruction.

Pathologically, the lesions may be found throughout the gastrointestinal tract from the esophagus to the rectum, and the term "enterocolitis" is inconclusive. Briefly, there is vascular dilatation involving the lamina propria and submucosa, capillary hemorrhages, edema, transmigration of leukocytes from adjacent vessels, epithelial degeneration and sloughing followed by fibrin deposition, which, with leukocytes, forms a membrane over the denuded mucosa. The muscularis is congested and focally hemorrhagic.[3, 47]

The onset is usually acute and severe with vomiting, fever, marked abdominal distention, diarrhea with or without blood, shock and, in fatal cases, a course of only 24 to 72 hours before death. Signs of tetany may be present. A history of previous antibiotic therapy, evidence of intestinal obstruction, or abdominal surgery prior to the onset of the acute symptoms may be important from a diagnostic standpoint. Direct stool smears or stool cultures may reveal staphylococcus; more often no pathogens are found. The usual rapid course of the disease in infants does not justify waiting for culture results in order to establish an etiologic diagnosis and institute antibiotic treatment.

Early heroic treatment may be lifesaving, and thus anticipation and early recognition of the disease are important. Decompression of the bowel, and treatment of shock with appropriate electrolyte solutions and plasma should be instituted. Intravenous calcium may be necessary. Possibly corticotropin, cortisone or hydrocortisone may be of value. Because of possible staphylococcus infection, erythromycin can be given while awaiting the results of stool cultures.

Regional Enteritis

Regional enteritis, a disease that occurs predominantly in adults, is being recognized with increasing frequency in children.[79] The etiology

remains obscure, in spite of the fact that the clinical course of the disease and the pathologic finding of inflammation suggest an infectious agent. Culture of stools, resected tissues, lymph nodes, mesentery and peritoneal fluid have consistently failed to reveal a specific organism. Only Felsen[25] was able to demonstrate specific organisms. He recovered *Shigella dysenteriae* or *S. paradysenteriae* from the stools of 12 patients and described this as appendiceal dysentery with normal appendix, mesenteric adenitis and terminal ileitis.

Although the onset of the disease in children is most often acute, resembling acute appendicitis, it may be insidious, and the course that of a low grade infection without specific complaints. Abdominal pain is usually present and may be cramping. Intermittent diarrhea is frequent, although constipation may intervene. Periods of pyrexia may occur, but a persistent low grade fever is more common. Weight loss is usual. The abdomen at some time is tender and may be slightly distended. Depending upon the chronicity of the disease and the extent of the underlying lesion, a mass may or may not be palpated in the abdomen, most often on the right side. Rarely, there is evidence of partial or complete intestinal obstruction.[35] Radiologic examination with barium, particularly fluoroscopy, usually will reveal changes in the lower ileum.

Recently Storrs and Hoekelman[79] emphasized that the disease in children is usually acute, is a nonrecurring process, and rarely progresses to the chronic form frequently seen in adults. They believe, as does Bargen,[1] that acute regional enteritis and chronic regional enteritis are not the same entity. The clinical picture in all their cases simulated that of appendicitis. Exploratory laparotomy and appendectomy were performed in each patient. In no patient was the bowel resected. A follow-up of seven patients for periods ranging from three to 13 years revealed that all have been completely free from symptoms referable to the gastrointestinal tract, and x-ray studies in six showed no evidence of disease. This is of extreme importance from a prognostic standpoint, since in adults only 25 per cent regress with healing, whereas 75 per cent progress to chronic regional ileitis.[16]

Since the disease often subsides spontaneously in children, in the absence of evidence of complications such as obstruction, hemorrhage, perforation and peritonitis, conservative management should be undertaken.[79] The use of hormone therapy is rarely justified by virtue of unproved curative effects and the fact that symptoms may be masked and the progress of the disease may be followed with less certainty.[54, 70] Recently Popp, Bargen and Dixon[66] of the Mayo Clinic reported improvement in almost 50 per cent of 50 patients after roentgen therapy. Results are best in the localized, hyperplastic form of the disease.

The general principles of medical management are as follows: bodily

rest, adequate nutrition, reduction of intestinal activity, correction of secondary systemic effects such as anemia, dehydration and hypoproteinemia and control of infection with sulfonamides and antibiotics.[43] Because of the prominence of allergic manifestations and severe emotional disturbances present in two of three patients observed recently by one of us (R.H.K.), it is suggested that attempts be made to alleviate these disturbing influences when they exist. There is the possibility that in certain cases, either or both of these factors may be of etiologic significance.

Chronic Ulcerative Colitis

Chronic ulcerative colitis is not uncommon in children[45] and has been found in newborn infants.[5] The etiology is obscure, and many factors are important in the clinical picture. Because of the inflammatory nature of the disease, like regional enteritis, some investigators believe that it has an infectious origin. Bacterial and viral infections, nutritional deficiencies and allergy have been suggested as causative factors.[45] Gross[30] states that bacteriologic studies made on many of his patients have revealed inconclusive results. Repeated cultures from stools and from lesions during proctoscopic examination in 11 patients observed in our hospital during the past five years failed to show pathogens. Bargen and Kennedy[2] noted that in the majority of their cases the onset as well as relapses occurred most often during the months when respiratory tract infections were prevalent. Neurogenic muscular spasm with secondary ulcerative changes has been suggested as an etiologic factor. Emotional or psychogenic disturbances may be contributory and often precipitating factors in the onset of the disease in many instances.[44, 45]

Bargen and Kennedy[2] state that in their experience the disease is more severe in children than in adults, and the response to treatment is less satisfactory. This is interesting in view of the fact that usually the opposite holds true in regional enteritis. In the 139 cases recently studied by Bargen and Kennedy[2] the disease was more common in boys, and the commonest age at the onset was 8.6 years, although in six children it occurred between one and two years. In only 10 did it occur between 13 and 14 years. In our 11 cases the youngest was three years; there were two, six years; two, eight years; one, 11 years; one, 12 years; three, 13 years; and one, 14 years of age.

The onset is usually insidious, with increased number of stools, and finally diarrhea. Although the disease started mildly in the majority of Bargen and Kennedy's cases, progression in severity was common. Only five were fulminating at onset. Mucus, pus and blood are intermixtures during the course of the disease, although, at the onset or early in the

disease, varying amounts of blood without mucus or pus are not uncommon. Occasionally, gross bleeding may be present at the onset. Tenesmus and abdominal cramps are often present. In the absence of complications abdominal distention ordinarily does not occur. A persistent low grade fever is not uncommon, and there may be spikes of high temperature. Anemia and weight loss occur. Depending upon the severity and duration of the disease, dehydration and electrolyte imbalance may result. Wasting and emaciation may be pronounced. When the disease develops in infancy and becomes chronic, retardation of growth and sexual development is common. This was noticeable in several of our 11 cases.

The diagnosis is established by proctoscopic examination and the typical roentgenographic appearance of the colon following a barium enema.[2, 30, 44, 46] It is extremely important that in all cases careful bacteriologic studies be performed, not only of the stools, but also from the lesions during proctoscopic examination to exclude bacillary dysentery, amebic dysentery and tuberculosis. A roentgenogram of the chest and tuberculin test will be of aid in excluding tuberculosis. A positive tuberculin test justifies gastric washings and stools for culture and guinea pig inoculation.

The disease in children is usually chronic, remissions and exacerbations occurring indefinitely. Complications are numerous and varied and include recurrent hemorrhage, electrolyte imbalance, rectal polyps, carcinoma, hepatitis and cirrhosis, arthritis, perirectal fistulas, failure of growth and sexual development.[2, 45] Complete recovery can be anticipated in approximately 40 to 50 per cent of the cases.[2]

The management of chronic ulcerative colitis in children may be obtained in detail by consulting recent articles by Bargen and Kennedy[2] and Kirsner and associates.[45] They state that a well ordered program is essential. This includes education, orientation, psychologic evaluation, psychiatric treatment when indicated, and proper dietary control. The patient should be kept in the hospital long enough for these important steps not only to be initiated, but also to be well under way. The parent as well as the child must be oriented and educated. Three important measures for active control of intestinal infections are antibiotics, Terramycin and chloramphenicol preferably,[2] or sulfonamides. Blood transfusions are also of value in combating anemia and hypoproteinemia. In the acute and severe stages fluid and electrolyte balance must be maintained. Adequate vitamin administration is necessary, particularly B complex. Cortisone and corticotropin are usually not recommended. The exception apparently is in resistant cases when they may reverse an unfavorable course and accelerate the recovery.[45] Five of our 11 cases received cortisone or corticotropin with little influence on the course of the disease. As in regional enteritis, these drugs

may mask the symptoms and particularly the complications. Finally, the diet should be high protein, high caloric and low residue. Surgery in children is rarely indicated and is usually performed only for complications.

Acknowledgment is made to Dr. Albert Milzer, Chairman of the Department of Microbiology of Michael Reese Hospital, and to Miss Helen MacLean, also of the same department, for their assistance in our bacteriologic studies.

REFERENCES

1. Bargen, J. A., discussion of Kiefer, E. D., and Ross, J. R.: Criteria in Management of Chronic Ileitis. *J.A.M.A.*, 129:104, 1945.
2. Bargen, J. A., and Kennedy, R. L. J.: Chronic Ulcerative Colitis in Children. *Postgrad. Med.*, 17:127, 1955.
3. Beatty, E. C., Jr., and Hawes, C. R.: Pseudomembranous Enterocolitis in Infancy. *J. Pediat.*, 46:654, 1955.
4. Beemer, A. M., Pryce, D. M., and Ridell, R. W.: Candida Albicans Infection of the Gut. *J. Path. & Bact.*, 68:359, 1954.
5. Beranbaum, S. L., and Waldron, R. J.: Chronic Ulcerative Colitis. *Pediatrics*, 9:773, 1952.
6. Block, L., Milzer, A., and Kerdeman, E.: Typhoid-Like Infection Due to Paracolon Bacillus. *Gastroenterology*, 12:509, 1949.
7. Braun, O. H., and Resemann, G.: Ueber das Vorkommen von E. coli 026:B6 and 086 bei der Säulingsenteritis. *Klin. Wchnschr.*, 30:853, 1952.
8. Bray, J.: Isolation of Antigenically Homozygous Strains of *Bact. Coli* Neopolitanum from Summer Diarrhea of Infants. *J. Path. & Bact.*, 57:239, 1945.
9. Brown, W. J., Winston, R., and Sommers, S. C.: Membranous Staphylococcal Enteritis after Antibiotic Therapy; Report of Two Cases. *J. Digest. Dis.*, 20:72, 1953.
10. Cherry, W. B., Lantz, P. L., and Barnes, L. A.: Implication of *Proteus Mirabilis* in an Outbreak of Gastroenteritis. *Am. J. Pub. Health*, 36:484, 1946.
11. Christie, A., Middleton, J. G., Peterson, J. C., and McVickar, D. L.: Treatment of Disseminated Histoplasmosis with Ethyl Vanillate. *Pediatrics*, 7:7, 1951.
12. Conant, N. F., Smith, D. T., Baker, R. D., Callaway, J. L., and Martin, D. S.: *Manual of Clinical Mycology*. 2nd ed. Philadelphia, W. B. Saunders Company, 1954.
13. Cooper, M. L., Walters, E. W., Keller, H. M., Sutherland, J. M., and Wiseman, H. J.: Epidemic Diarrhea among Infants Associated with the Isolation of *Escherichia Coli*: E. Coli 0127:B8. *Pediatrics*, 16:215, 1955.
14. Craig, C. F.: *The Etiology, Diagnosis and Treatment of Amebiasis*. Baltimore, Williams & Wilkins Company, 1944.
15. Cramer, R., and Rossi, E.: Vomiting and Diarrhea with Fatal Circulatory Collapse in Children Following Treatment with Chloromycetin and Terramycin: Discussion of Staphylococci Enteritis. *Helvet. paediat. acta*, 8:544, 1953. Abstracted, *J.A.M.A.*, 155:790, 1954; *Year Book of Pediatrics*, Chicago, Year Book Publishers, Inc., 1955, p. 407.
16. Crohn, B. B., in discussion of Storrs and Hoekelman: Acute Regional Enteritis in Children, in *Year Book of Pediatrics*. Chicago, Year Book Publishers, Inc., 1954, p. 20.
17. D'Antoni, J. S.: Standardization of the Iodine Stain in Wet Preparations of Intestinal Protozoa. *Am. J. Trop. Med.*, 17:79, 1937.
18. D'Antoni, J. S.: Essential Considerations of the Chronic Diarrheas. *New Orleans M. & S.J.*, 101:478, 1949.
19. De Silva, P. C. C.: Amoebiasis in Infancy. *Brit. M.J.*, 2:1208, 1949.
20. Dixon, C. F., and Weisman, R. E.: Acute Pseudomembrane Enteritis or Entero-

colitis: A Complication Following Intestinal Surgery. *S. Clin. North America*, 28:999, 1948.
21. Edwards, P. R., West, M. G., and Bruner, D. W.: The Serologic Classification of the Arizona Group of Paracolon Bacteria. *J. Infect. Dis.*, 81:19, 1947.
22. Fairlie, C. W., and Randall, R. S.: Fatal Staphylococcus Enteritis Following Penicillin and Streptomycin Therapy. *J.A.M.A.*, 153:90, 1953.
23. Faust, E. C., and Headlee, W. H.: Intestinal Parasite Infections of the Ambulatory White Population of New Orleans. *Am. J. Trop. Med.*, 10:25, 1936.
24. Feig, M.: Epidemic Shigella Gastroenteritis (Bacillary Dysentery) in an Endemic Area. II. Age-Specific Clinical Aspects. *Pediatrics*, 11:145, 1953.
25. Felsen, J.: Appendicular Form of Bacillary Dysentery, with Notes on Mesenteric Adenitis and Inflammation of Distal Portion of Ileum. *Am. J. Dis. Child.*, 50,661, 1935.
26. Finland, M., Grigsby, M. E., and Haight, T. H.: Efficacy and Toxicity of Oxytetracycline (Terramycin) and Chlortetracycline (Aureomycin). *Arch. Int. Med.*, 93:23, 1954.
27. Garland, J.: Editorial: Antibiotics, Staphylococcal Enteritis, and Pseudomembranous Enterocolitis. *New England J. Med.*, 249:37, 1953.
28. Giles, C., Sangster, G., and Smith, J.: Epidemic Gastroenteritis of Infants in Aberdeen during 1947. *Arch. Dis. Childhood*, 24:45, 1949.
29. Goldenberg, C., Shlaes, W. H., and Mentzer, S.: A Clinical Report on Amebiasis in Infants under One Year of Age. *J. Pediat.*, 40:290, 1952.
30. Gross, R. E.: *The Surgery of Infancy and Childhood*. Philadelphia, W. B. Saunders Company, 1953, p. 316.
31. Harrison, H. E.: The Treatment of Diarrhea in Infancy. PEDIAT. CLIN. NORTH AMERICA, 1:335, 1954.
32. Hay, P., and McKenzie, P.: Side-Effects of Oxytetracycline Therapy. *Lancet*, 1: 945, 1954. Abstracted, *Year Book of Pediatrics*, Chicago, Year Book Publishers, Inc., 1955, p. 405.
33. Henderson, R. G., Pinkerton, H., and Moore, L. T.: *Histoplasma Capsulatum* as a Cause of Chronic Ulcerative Enteritis. *J.A.M.A.*, 118:885, 1942.
34. Heymann, W.: Metabolism Studies on Age Disposition to Ketosis in Human Beings. *J. Pediat.*, 12:21, 1938.
35. Howard, W. K., Pulaski, E. J., and Morrissey, R. W.: Regional Enteritis in Children: Report of Two Cases. *J. Pediat.*, 46:298, 1955.
36. Howell, K. M., and Knoll, E. W.: Amebiasis in Infants and Children. *Am. J. Dis. Child.*, 61:54, 1941.
37. Hunter, C. A., and Ensign, P. R.: An Epidemic of Diarrhea in a New-Born Nursery Caused by *Pseudomonas Aeruginosa*. *Am. J. Pub. Health*, 37:1166, 1947.
38. Jawetz, E.: Infections with *Pseudomonas Aeruginosa* Treated with Polymyxin B. *Arch. Int. Med.*, 89:90, 1952.
39. Kagan, B. M., Krevsky, D., Milzer, A., and Locke, M.: Polymyxin B and Polymyxin E. *J. Lab. & Clin. Med.*, 37:402, 1951.
40. Kaliski, S. R., and Geppert, L. J.: Diarrhea in San Antonio; Analysis of 1,000 Hospital Cases. *Texas State J. Med.*, 50:477, 1954.
41. Kauffman, F.: *The Differentiation of Escherichia and Klebsiella Types*. Springfield, Ill., Charles C Thomas, 1951.
42. Kempe, C. H.: The Use of Antibacterial Agents. *Pediatrics*, 15:221, 1955.
43. Kiefer, E. D., Marshall, S. F., and Brolsma, M. P.: Management of Chronic Regional Enteritis. *Gastroenterology*, 14:118, 1950.
44. Kirsner, J. B., Palmer, W. L., Maimon, S. N., and Ricketts, W. E.: Clinical Course of Chronic Nonspecific Ulcerative Colitis. *J.A.M.A.*, 137:922, 1948.
45. Kirsner, J. B., Raskin, H. F., and Palmer, W. L.: Ulcerative Colitis in Children. *Am. J. Dis. Child.*, 90:141, 1955.
46. Kleckner, M. S.: Chronic Ulcerative Colitis—Proctologic Interpretation and Treatment. *J.A.M.A.*, 133:998, 1947.
47. Kleckner, M. S., Bargen, J. A., and Bagenstoss, A. H.: Pseudomembranous En-

terocolitis: Clinicopathologic Study of Fourteen Cases in Which the Disease Was not Precipitated by an Operation. *Gastroenterology*, 21:212, 1952.
48. Kunstadter, R. H., and Breslow, L.: Diarrhea in Infancy. *Gen. Practitioner*, 3:51, 1951.
49. Kunstadter, R. H., Milzer, A., and Kagan, B. M.: Chloramphenicol and Terramycin in the Treatment of Salmonella and Shigella Infections. *J. Pediat.*, 39: 687, 1951.
50. Levinson, J. D., and Raycraft, W. B.: A Study of Three Hundred Cases of Diarrhea in Infants and Children during the Summer and Fall of 1948. *J. Pediat.*, 36:316, 1950.
51. Lieberman, D., and Jawetz, E.: Treatment of Chronic Shigella Infection in Children with Oral Polymyxins. *Pediatrics*, 8:249, 1951.
52. Light, J. S., and Hodes, H. L.: Studies on Epidemic Diarrhea of the Newborn: Isolation of a Filtrable Agent Causing Diarrhea in Calves. *Am. J. Pub. Health*, 33:1451, 1953.
53. Loeber, M., and D'Antoni, J. S.: Some Recent Experiences with Amebiasis in Children. *New Orleans M. & S.J.*, 100:276, 1947.
54. Machella, T. E., and Hollan, O. R.: Effect of Cortisone on Clinical Course of Chronic Regional Enteritis and Chronic Idiopathic Ulcerative Colitis. *Am. J.M. Sc.*, 221:501, 1951.
55. Manson-Bahr, P.: *Dysenteric Disorders*. London, Casell & Co., Ltd., 1944, p. 123.
56. Milzer, A., MacLean, H., and McElwaine, N.: Treatment of Intestinal Infections Associated with Low Grade Pathogenic Bacteria. *Rev. Gastroenterology*, 16:122, 1952.
57. Morgan, H. de R.: Upon the Bacteriology of the Summer Diarrhoea in Infants. *Brit. M.J.*, 1:908, 1906.
58. Murphy, W. J., and Morris, J. F.: Two Outbreaks of Gastroenteritis Apparently Caused by a Paracolon of the Arizona Group. *J. Infect. Dis.*, 86:255, 1950.
59. Neter, E., and Farrar, R. H.: *Proteus Vulgaris* and *Proteus Morganii* in Diarrheal Disease of Infants. *Am. J. Digest. Dis. & Nutrition*, 10:344, 1943.
60. Neter, E., and Shumway, C. N.: E. Coli Serotype D433: Occurrence in Intestinal and Respiratory Tract, Cultural Characteristics, Pathogenicity, Sensitivity to Antibiotics. *Proc. Soc. Exper. Biol. & Med.*, 75:504, 1950.
61. Neter, E., Gorzynski, A., Zalewski, J., Rachman, R., and Gino, R. M.: Studies on Bacterial Hemagglutination. *Am. J. Pub. Health*, 44:49, 1954.
62. Nyhus, R. E., and Burke, E. C.: Pseudomembranous Enterocolitis: Medical Treatment, with Recovery. *Proc. Staff Meet., Mayo Clin.*, 29:513, 1954.
63. Orskov, F.: On Occurrence of E. Coli Belonging to O-Group 26 in Cases of Infantile Diarrhea and White Scours. *Acta path. et microbiol. Scandinav.*, 29:373, 1951.
64. Peterson, J. C., and Christie, A.: Histoplasmosis. PEDIAT. CLIN. NORTH AMERICA, 2:139, 1955.
65. Pickering, D. E., and Winters, R. W.: Fluid and Electolyte Management in Children. PEDIAT. CLIN. NORTH AMERICA, 1:873, 1954.
66. Popp, W. C., Bargen, J. A., and Dixon, C. F.: Regional Enteritis: Roentgen Therapy. *Proc. Staff Meet., Mayo Clin.*, 25:1, 1950.
67. Pratt, E. L.: Fluid and Electolyte Therapy. PEDIAT. CLIN. NORTH AMERICA, 2:317, 1955.
68. Putnam, H. C., Jr., Dockerty, M. B., and Waugh, J. M.: Abdominal Actinomycosis. An Analysis of 122 Cases. *Surgery*, 28:781, 1950.
69. Raftery, A.: Subclinical Histoplasmosis. Gastrointestinal Histoplasmosis of Children. *J.A.M.A.*, 145:216, 1951.
70. Saner, W. G., Brown, P. W., and Dearing, W. H.: Experiences and Use of Corticotropin in Regional Enteritis. *Gastroenterology*, 22:550, 1952.
71. Saphra, I.: Fatalities in Salmonella Infections. *Am. J.M. Sc.*, 220:74, 1950.
72. Shanks, R. A., and Studzinski, L. P.: Bact. Coli in Infantile Diarrhoea. *Brit. M.J.*, 2:119, 1952.

73. Shrapnel, B. C., Johnson, C. M., and Sandground, J. H.: Oral Emetine in Treatment of Intestinal Amebiasis. *Am. J. Trop. Med.*, 26:293, 1946.
74. Shull, H. J.: Human Histoplasmosis. A Disease with Protean Manifestations Often with Digestive System Involvement. *Gastroenterology*, 25:582, 1953.
75. Singer, J. M., Bar-Hay, J., and Hoenigsberg, R.: The Intestinal Flora in the Etiology of Infantile Infectious Diarrhea. *Am. J. Dis. Child.*, 89:531, 1955.
76. Smith, J.: Association of Certain Types (A and B) of *Bact. Coli* with Infantile Gastroenteritis. *J. Hyg.*, 47:221, 1949.
77. Smith, J., and Galloway, W. H.: Sensitivity to Antibiotics of Strains of *Bacterium Coli* Associated with Infantile Gastroenteritis. *Arch. Dis. Childhood*, 28:30, 1953.
78. Stanley, M. M.: Bacillus Pyocyaneus Infections. *Am. J. Med.*, 2:253, 347, 1947.
79. Storrs, R. C., and Hoekelman, R. A.: Acute Regional Enteritis in Children. *New England J. Med.*, 248:320, 1953.
80. Stuart, C. A., and Rustigian, R.: Further Studies on One Type of Paracolon Organism. *Am. J. Pub. Health*, 33:1323, 1943.
81. Taubenhaus, L. J.: Amebiasis in Infants and Young Children. *North Carolina M.J.*, 11:236, 1950.
82. Taylor, J., Powell, B. W., and Wright, J.: Infantile Diarrhoea and Vomiting. *Brit. M.J.*, 2:117, 1949.
83. Wheeler, W. E., and Wainerman, B.: The Treatment and Prevention of Epidemic Infantile Diarrhea Due to E. Coli O-111 by the Use of Chloramphenicol and Neomycin. *Pediatrics*, 14:357, 1954.
84. Wolfish, M. G.: Acute Gastroenteritis. *J. Pediat.*, 43:675, 1953.
85. Winter, W. D.: Candida (Monilia) Infections in Children. PEDIAT. CLIN. NORTH AMERICA, 2:152, 1955.

29th Street and Ellis Avenue
Chicago 16, Illinois

PRACTICAL MANAGEMENT OF TUBERCULOSIS

MARGARET H. D. SMITH, M.D.

Should every child with a positive tuberculin test be treated with chemotherapeutic agents? Or should these drugs be reserved for the more serious complications of tuberculosis? When drug treatment is decided upon, which are the drugs and the treatment schedule of choice?

It will be some years before we can answer these questions with assurance. The following paragraphs represent an attempt to answer them in the light of past experience with the course and evolution of tuberculosis in children, and recent observations on chemotherapy.

IMPORTANT PROGNOSTIC FACTORS

It has long been known that certain factors are of particular importance in evaluating the probable course and outcome of tuberculosis in a particular child.

Age at the Time of Infection

Age at the time of infection appears to be the most important single factor. Thus Brailey,[3] in a study of the mortality of tuberculin-positive infants, found that the mortality was more than twice as high in infants known to have been infected during the first six months of life as in those whose infection was discovered between the ages of six months and two years. Le Melletier[13] found a mortality of 30 per cent for infants infected before six months of age, 14 per cent for children

From the Department of Pediatrics, New York University College of Medicine, and the Chest Clinic of the Children's Medical Service, Bellevue Hospital, New York City.

infected between six months and one year, and 7 per cent for children between one and two years. Of these deaths, as Lincoln[14] has shown, most are due to tuberculous meningitis or miliary tuberculosis, a few to progressive primary tuberculosis or the protracted hematogenous form. In children between the ages of two or three years and 13 years, deaths due to tuberculosis are uncommon. However, the risk of progressive tuberculous disease rises sharply in girls at 12 to 13 years and in boys at 15 years, and this high morbidity persists for three to five years thereafter. Lincoln* found reactivation of previously quiescent tuberculosis in 9 per cent of the children followed in her clinic; it occurred twice as often in girls as in boys. The statistics of Meyer,[18] Frölich[9] and Hyge[11] in Scandinavia and of Besançon and Rollin[2] in France show the seriousness of tuberculous infection at adolescence, regardless of whether the infection is freshly acquired at that time or whether it had been acquired earlier in childhood. Curiously enough, the chances for developing active tuberculous disease seem to be about 10 per cent in either case, although Opie, McPhedran and Putnam[20] found that no less than 20 per cent of persons first exposed to infection between the ages of 10 and 14 years went on to show clinical evidence of disease.

Size of the Infecting Dose

It is impossible in human beings to prove that the size of the infecting dose plays an important part in the evolution of the disease, yet there is suggestive evidence: Frölich[9] found the mortality to be three times as high when the infection was acquired within the home. Holmdahl[10] found a higher incidence of complications when the contact was familial, and many others have made similar observations, suggesting that repeated daily contact with an infected person is apt to be more serious than casual contact.

Age of the Infection When First Diagnosed

It has long been known that in childhood the first six months after infection are the most dangerous so far as progressive disease is concerned. Most of the serious complications occur within the first year of infection, so that a child who is in good health at the end of that time will probably not suffer one of the grave complications of primary tuberculosis, in particular, miliary or meningeal disease.

CHEMOTHERAPY: GENERAL CONSIDERATIONS

Streptomycin has proved to be an extremely effective antituberculous drug, particularly when used in combination with para-aminosalicylic

* Personal communication.

acid (PAS) to retard the emergence of drug-resistant organisms. However, short courses of treatment with these drugs were followed in many cases by serious recrudescences of disease, often due to drug-resistant strains, so that the tendency has been to extend the time of treatment. Even after intensive treatment it is not possible to eradicate completely tubercle bacilli with these drugs, as shown by the occurrence of tuberculous meningitis even after prolonged streptomycin administration for tuberculous disease elsewhere in the body. So troublesome is the matter of drug resistance to streptomycin that this drug should probably *never* be used as the sole tuberculostatic agent.

The high degree of toxicity which streptomycin displays for the eighth nerve, the unpleasantness of repeated intramuscular injections, the nausea induced in some patients by PAS and the occasional occurrence of meningitis despite therapy have made the combination of streptomycin and PAS justifiably less popular in children than isoniazid. The two drugs may be useful in patients with tubercle bacilli resistant to isoniazid, or in patients treated at home where the family cannot be relied on to give isoniazid by mouth, whereas the visiting nurse can administer the streptomycin. Furthermore, streptomycin and PAS are frequently given for a short time (i.e., several weeks) to "cover" surgical operations such as tonsillectomy, removal of cervical glands, and the like in patients whose disease is quiescent, but in whom the operation itself might cause a sudden spillage of tubercle bacilli.

Isoniazid can be given orally as tablets or as a flavored syrup, and likewise intramuscularly in the same dosage: thus it immediately presents an advantage over streptomycin. Though isoniazid-resistant strains of tubercle bacilli do emerge, they take longer to become clinically significant than with streptomycin. The concomitant administration of PAS retards drug resistance just as it does with streptomycin. Nevertheless many competent investigators feel that PAS should not be given together with isoniazid, since isoniazid alone is relatively very effective. They prefer to reserve the streptomycin-PAS combination for possible "emergencies" later in the course of the disease.[8] Isoniazid may be given together with Promizole as recommended by Lincoln.[15] However, the outstanding advantage of isoniazid at the moment in children seems to be its ability to prevent the development of tuberculous meningitis.[15] Isoniazid is so nontoxic that, although daily doses of 5 to 10 mg. per kilogram are usually recommended, doses of 20 to 30 mg. per kilogram have been given to patients with tuberculous meningitis with beneficial effects.[6]

Viomycin may be used as a last resort in patients resistant to both streptomycin and isoniazid. In doses of 15 to 20 mg. per kilogram daily, or 30 mg. per kilogram twice weekly, it is fairly well tolerated. Renal

and eighth nerve damage, skin eruptions and depletion of electrolytes are among the undesirable effects produced by viomycin.

OUTLINE FOR EVALUATION OF A POSITIVE TUBERCULIN TEST

When a child of any age, from infancy through adolescence, is found to have a positive tuberculin test, the situation can best be evaluated on the basis of clinical and radiologic findings, if a certain routine is followed: (1) tuberculin skin test, (2) roentgenogram of the chest, (3) history of contact, especially familial, (4) symptoms, (5) physical examination, and (6) gastric lavage.

1. Tuberculin Skin Test

Was the tuberculin test really positive? If the test was performed and read by someone else, we believe that the physician who is to be responsible for the child's supervision should repeat the test himself, using Old Tuberculin diluted 1:10,000 ("0.01 mg."), or no more than 0.0002 mg. of Purified Protein Derivative ("first strength PPD"). The test should be read in 48 or 72 hours; a positive test consists of an area of *induration* at least 5 mm. in diameter. If the induration is less, or if erythema only is present, then a test with a more concentrated tuberculin or PPD is indicated. The only serious contraindication to repeating a diagnostic tuberculin test is disease of the eye: tuberculosis of the eye is usually associated with a high degree of hypersensitivity, and serious damage to the eye may ensue.

2. Chest Roentgenogram

Does the child display radiologic evidence of tuberculosis? "An x-ray film, technically perfect and correctly interpreted, if judged in conjunction with the results of the tuberculin test, is the most reliable aid we have towards the diagnosis, prognosis and treatment of primary tuberculosis."[21] Since tubercle bacilli enter the body in most cases by inhalation, the chest is the site most frequently affected. The initial focus in the lung is so small that it is never detected until extensive bacillary multiplication has taken place, with invasion of the lymphatic channels and nodes draining that area. Consequently, enlargement of the hilar lymph nodes on a roentgenogram suggests tuberculosis. Such enlargement should always be looked for on both postero-anterior and lateral views of the chest. If a lesion is present, then evidence of activity or healing is sought.

3. History of Contact

Is there a history of heavy exposure? of recent contact? If the exposure is to a sputum-positive adult in the household, the disease may run a more severe course in the child. A history of recent contact may be associated with a negative roentgenogram in a tuberculin-positive child; if such a situation is suspected, roentgenograms should be repeated at monthly intervals for three months.

4. Symptoms

Have the parents noticed fever in the child, loss of appetite, fatigue or a brassy cough? The presence of such symptoms in a tuberculin-positive child suggests that the disease is still in the active stage. The bitonal cough in particular suggests compression somewhere in the tracheobronchial tree by an enlarged mediastinal node, with this exception—cough in children is usually *not* a manifestation of tuberculosis.

5. Physical Examination

Does the physical examination yield suggestive evidence of tuberculous infection? Nontender enlargement of the cervical lymph glands, general glandular enlargement and splenic enlargement, if present, are evidence in favor of an active tuberculous infection. Papulonecrotic tuberculids and phlyctenular conjunctivitis provide strong evidence in this direction. Examination of the chest rarely yields evidence of disease.

6. Gastric Lavage

Are tubercle bacilli present in the gastric washings? Since children rarely cough, resort must be had to stomach washings for the purpose of demonstrating tubercle bacilli. The stomach should be washed out in the very early morning and the material concentrated and cultured on suitable media. This procedure is of value in doubtful cases, in determining the activity of a clear-cut case and in evaluating the progress of the disease under treatment.

THE CHILD WITH A POSITIVE TUBERCULIN TEST AND NO RADIOLOGIC EVIDENCE OF DISEASE

The Infant under 18 Months

It seems clear that any child in this age group with a positive tuberculin test has acquired the disease rather recently; therefore the disease

is active. Moreover, he probably acquired it from a parent, grandparent, nurse or other household contact, and consequently probably received a large dose of tubercle bacilli. In this age group, therefore, it seems wise to give all children with positive tuberculin tests isoniazid in a dose of 10 mg. per kilogram of body weight daily. This can be given in the form of syrup of isoniazid, divided into two daily doses, and is well tolerated. The duration of treatment is at present purely empirical: six months is probably adequate. Para-aminosalicylic acid may be added, but it is probably much wiser to "save" this drug for use together with streptomycin, should complications of the disease arise.[8]

The Child between 18 Months and Puberty

Concerning the advisability of chemotherapy in this age group there is at present the widest divergence of opinion. The prognosis for these children is good; there is evidence that tubercle bacilli which are not multiplying rapidly are less susceptible to the action of chemotherapeutic agents; and Schmidt's[22] investigations in monkeys suggest that chemotherapy of inapparent infections may hamper development of immunity. On the other hand, eradication of tuberculous infection as manifested by tuberculin conversion may be possible and desirable. Since effective chemotherapeutic agents are available in case of complications, it is our policy at present not to treat these patients. In either case the children should be given the benefit of good care and good nutrition. It is probably wise to limit violent physical activity, particularly competitive activity. Since measles and whooping cough seem to exert a deleterious effect on tuberculosis, at least on recently acquired tuberculosis, suitable measures should be taken to prevent them: active immunization against whooping cough, and gamma globulin on exposure to measles. The patient should be seen by the physician every month or two at first; later every three months. After a year has passed, the danger of complications decreases greatly, and both supervision and restrictive measures may be relaxed. It should be pointed out, however, that others disagree with this view.[7, 17, 24]

The Child at Puberty

Whether children who have positive tuberculin tests at this age should receive chemotherapy routinely is not at all clear. Our policy at present is to follow them up every three months with chest roentgenograms, and to pay particular attention to temperature, weight and appetite. Johnston's[12] studies on adolescent girls have made it amply clear that a generous intake of protein and calcium at this age is of prime importance in controlling pulmonary tuberculosis.

THE CHILD WITH A POSITIVE TUBERCULIN TEST AND ENLARGED HILAR LYMPH NODES

Infection of the tracheobronchial lymph nodes is frequent, indeed, in children with tuberculosis. Often there are no symptoms; or the symptoms are vague, consisting of irregular low grade fever, fatigue, irritability, failure to gain, and vague aches and pains. Healing usually takes place slowly by fibrosis and often calcification. Calcification may appear within a year of infection, or it may be delayed for two or three years.

We believe that all children under the age of 18 months with this form of tuberculosis should receive isoniazid unless the lesion is already well healed at the time of diagnosis. Not that isoniazid exerts any striking effect at all on the course of the mediastinal lesion: the nodes cannot be expected to decrease in size any more rapidly with isoniazid than without it. Under these circumstances isoniazid is given purely for its prophylactic effect on the lethal tuberculous complications which arise, as we know, in a considerable number of cases.

Children between the ages of 18 months and puberty with nonprogressive primary tuberculosis should be under regular medical supervision and should have the best possible nutrition, adequate rest, and so on. But so long as they display no fever, malaise or loss of weight, children with this type of tuberculosis may safely lead normal, unrestricted lives, go to school and engage in full activity.

THE CHILD WITH CERVICAL ADENITIS

Infection of the cervical lymph nodes is probably most often secondary to tuberculous infection of the tonsils. It is seen rather infrequently in this country today because of the virtual disappearance of bovine tuberculosis. It is, however, still seen in infants or very young children on the one hand, or in adolescent girls on the other. Diagnosis is based on the presence of a positive tuberculin test, isolation of tubercle bacilli on smear or culture of the drainage or aspirate of the node, or on the basis of the histologic characteristics of an excised lymph node.

Treatment depends on the character of the nodes at the time of diagnosis. If they are discrete, excision is the ideal procedure, either isoniazid or streptomycin and PAS being given for several days before and some weeks after the operation. If the lymph nodes have liquefied and the caseous contents have ruptured through the capsule, with consequent discoloration of the overlying skin, then the area should be incised and irrigated with a solution of the enzymes streptokinase and streptodornase. Irrigations are carried out at first once or three times daily, later every two days. Between irrigations the cavity is packed

with gauze saturated with enzyme solution. After three to five weeks healing occurs with minimal scar formation.[16]

Tonsillectomy has been recommended for all patients with cervical adenitis, but its value has never been established. Antimicrobial therapy of tuberculous lymph nodes has, on the whole, been disappointing. Sometimes, when the nodes are first seen as a rather firm, discrete mass, they disappear under chemotherapy. This is particularly true in adolescent patients.

Chemotherapeutic agents, preferably isoniazid, should nevertheless be used in these patients to prevent possible spread of the disease within the patient, and also, in open cases, to render the patient as quickly noninfectious to others as possible.

THE CHILD WITH PROGRESSIVE PRIMARY PULMONARY TUBERCULOSIS

Should the disease progress locally, as manifested by increased pulmonary involvement, bronchogenic spread to another part of the lung, or cavitation, then hospital or sanatorium care is advisable. Isoniazid is usually the drug of choice, though in rapidly progressive cases which are not responding to isoniazid and general measures it may be necessary to add streptomycin and PAS. If cavitation is present, the disease is considered active until cultures from gastric washings have been negative, cavities closed and roentgenograms stabilized for a period of six months. In children, as in adults, surgical removal of diseased lung segments may greatly speed recovery.

THE CHILD WITH MILIARY OR PROTRACTED HEMATOGENOUS TUBERCULOSIS

During the first two years of life heavy seeding of the blood stream with tubercle bacilli gives rise to miliary tuberculosis, which is usually fatal. In older children, however, less fulminating forms are apt to occur, giving rise to protracted and recurrent febrile episodes, and often associated with metastases to distant organs, or to hemic lung foci which are apt to pave the way for pulmonary tuberculosis in adult life.

These hematogenous forms of tuberculosis should probably be treated more intensively than progressive primary disease, not only because it is, untreated, usually fatal, but because the intense dissemination of tubercle bacilli throughout the body may give rise in later life to pulmonary, renal and osseous complications. This is a fact which we are only now beginning to realize. We therefore recommend treating these patients with isoniazid (10 to 20 mg. per kilogram daily) for eight to 12 months, PAS (0.5 gm. per kilogram daily) for at least a year, and streptomycin sulfate intramuscularly daily (50 mg. per

kilogram) for four to six weeks. As always in tuberculosis, adequate nutrition and fluids must be provided; anemia severe enough to warrant transfusion is sometimes present.

In following up these patients during convalescence and after apparent recovery, particularly at puberty, attention should be paid to the possible appearance of metastatic forms of tuberculosis involving the lungs, kidneys, lymph glands and bones.

THE CHILD WITH TUBERCULOUS MENINGITIS

The outcome in tuberculous meningitis depends so much on the stage of the disease at which effective treatment is instituted that no time should be lost in establishing the diagnosis as quickly as possible. The presence of a lymphocytic meningitis, sterile on ordinary culture media, with a cerebrospinal fluid sugar of 35 mg. per 100 cc. or below, in a child with a positive tuberculin test, is almost overwhelming evidence of tuberculous meningitis. Two to three days should suffice to establish these facts. Treatment should then be started using the three most effective antituberculous drugs available in the maximal dosage recommended for the treatment of miliary tuberculosis. Because of the slow healing of meningeal tuberculosis, it seems wise to prolong the administration of all the drugs, continuing streptomycin biweekly from the second to the sixth month, isoniazid for a year, and PAS for 18 months. When therapy has been delayed until the patient is already in coma, more intensive therapy, as used by Cocchi[6] with excellent results, may be recommended: his regimen includes intravenous dihydrostreptomycin (300 to 500 mg. daily) for the first week or so, also intrathecal streptomycin sulfate (20 to 30 mg. daily) and intrathecal isoniazid (20 to 40 mg. daily).

Patients in whom the free circulation of cerebrospinal fluid becomes blocked during the course of the disease present a serious problem, particularly if the block occurs in the region of the aqueduct or foramina (spinal blocks are less serious and often resolve spontaneously). *Tuberculin*, given intrathecally as very dilute PPD, has been helpful in the experience of some.[4] *Fibrinolytic enzymes* (streptokinase and streptodornase) also have been given intrathecally with doubtful effect upon the exudate.[5] *Cortisone* (in oral or intramuscular doses of 25 to 50 mg. daily) is highly recommended by Cocchi[6] and by Shane and Riley,[23] who have used it with excellent results.

In any case of tuberculous meningitis in which the diagnosis is made before the end stages of the disease, the outlook for full recovery is good, provided intensive treatment is started immediately and is carried through. It cannot be overemphasized that successful treatment depends not only on *starting* the treatment, but on *following* the pa-

tient with care: nutrition, hydration, electrolyte balance, anemia, prevention of contractures and bed sores, treatment of intercurrent infections of the skin and respiratory tract, occupational therapy and schooling for the convalescent are some of the important problems which must be considered from time to time in any child hospitalized for months, as these children are bound to be.

TUBERCULOSIS OF BONES AND JOINTS

Antimicrobial therapy administered early in the course of tuberculous disease of the joints, in particular, has greatly decreased the incidence of later crippling deformities. Late in the course of the disease antimicrobial therapy cannot reverse the extensive tissue destruction which has occurred, but it may make possible earlier surgical intervention. Immobilization remains one of the most important facets of treatment of the child with osseous tuberculosis.

SPECIAL PROBLEMS

A number of questions are frequently asked of the physician who is taking care of tuberculous children, or come to his mind in arranging for the patient's care.

Source of the Disease

Where did the child get his tuberculosis? This question opens the way for better education of the family and to the search for contacts. Since tuberculosis is essentially a familial disease, and since children in particular usually become infected in the home, the physician is responsible for tracking down not only the "source case," but also others who may have been infected within the family circle. Parents, grandparents, boarders, regular visitors, servants and "baby-sitters" must be investigated as possible sources of infection; and the other children in the family should be tuberculin-tested to discover whether they too are infected.

Removal from Infectious Contacts

Should the infected child be removed from contact with an infectious adult? The answer given to this question has almost always been: "Ideally, yes." However, statistics on this point are unsatisfactory. Recently Bentley and Gryzbowski[1] found no evidence, in their series of carefully studied patients, that removal from infection improved the prognosis. It seems, indeed, quite possible that the tubercle bacilli which are already multiplying within the child constitute a hazard beside which the danger from outside sources is negligible.

Is the Child with Tuberculosis Infectious to Others?

The child with cavitating tuberculosis who is coughing forth tubercle bacilli is undoubtedly just as infectious as any adult. The child with a draining sinus or with open, draining lymph nodes also constitutes a menace to others. But long years of experience have shown that the child with primary tuberculosis, even though he has tubercle bacilli in his stomach, is not infectious to his surroundings. Wallgren[19] has long supported this viewpoint, and those who have dealt extensively with tuberculosis in children generally agree with him.

BCG for Children in Contact with Tuberculosis

The efficacy of BCG in raising resistance to tuberculous infection seems so well established that we believe that it should be given to all children who must live in contact with cases of tuberculosis which are potentially or actively infectious. Among the former are principally adults with "arrested" tuberculosis, who may nevertheless occasionally cough up a few tubercle bacilli, or whose disease may again at any time become "active."

CONCLUSION

The child who has been infected with tubercle bacilli, whether the infection be manifested by a detectable disease process or only by a positive tuberculin test, should be supervised with particular care during infancy, or during the first year following his infection, and again during adolescence. Antimicrobial drugs should be given to those children who show evidence of serious disease or who stand in particular danger from spreading disease (e.g., young infants, tuberculous children undergoing surgical procedures, and so forth). All three of the most effective antituberculous drugs should be given to patients with miliary tuberculosis and tuberculous meningitis, but we believe it better to use only one or two of these drugs at a time for children suffering from less serious forms of the disease. All children with tuberculous infection should be given the benefit of adequate rest, good nutrition and immunization against whooping cough and measles, which constitute a particular hazard to them. These time-honored, relatively simple therapeutic measures suffice to bring about recovery in most cases.

REFERENCES

1. Bentley, F. J., Gryzbowski, S., and Benjamin, B.: *Tuberculosis in Childhood and Adolescence*. London, National Association for the Prevention of Tuberculosis, 1954.

2. Besançon, A., and Rollin: Une épidemie tuberculeuse dans un milieu scolaire. *Rev. Tuberc. Paris*, 15:608, 1951.
3. Brailey, M.: Mortality in Tuberculin Positive Infants. *Bull. Johns Hopkins Hosp.*, 59:1, 1936.
4. Cairns, H., Smith, H. V., and Vollum, R. L.: Tuberculous Meningitis. *J.A.M.A.*, 144:92, 1950.
5. Cathie, I. A. B.: Streptomycin-Streptokinase Treatment of Tuberculous Meningitis. *Lancet*, 1:441, 1949.
6. Cocchi, C.: Cortisone and ACTH in the Treatment of Tuberculosis in Infancy and Childhood, in *Proceedings of the International Symposium on Tuberculosis in Infancy and Childhood*. To be published.
7. Debré, R., and Brissaud, H. E.: Faut-il traiter la tuberculose initiale de l'enfant et de l'adolescent? *Presse méd.*, 62:523, 1954.
8. Deutschle, K., Ormond, L., Elmendorf, D., Jr., Muschenheim, C., and McDermott, W.: The Course of Pulmonary Tuberculosis during Long term, Single Drug (Isoniazid) Therapy. *Am. Rev. Tuberc.*, 70:228, 1954.
9. Frölich, T.: Im Jahre 1912 vorgenommene Untersuchungen über die Haeufigkeit der tuberkulöse Infektion unter den Schulkindern Oslos. Nachuntersuchung im Jahre 1925. *Acta paediat.*, 7:191, 1927–8.
10. Holmdahl, K.: Course and Prognosis in Primary Tuberculosis with Erythema Nodosum in Children. *Acta tuberc. Scandinav.*, supp. 12, 1950.
11. Hyge, T. V.: The Efficacy of BCG Vaccination. *Acta tuberc. Scandinav.*, 23:153, 1949.
12. Johnston, J. A.: *Nutritional Studies in Adolescent Girls and Their Relation to Tuberculosis*. Springfield, Ill., Charles C Thomas, 1953.
13. Le Melletier, J.: Pronostic de la tuberculose du nourrisson soustrait au contact infectant en dehors des antibiotiques. *Pédiatrie*, 40:169, 1951.
14. Lincoln, E. M.: Course and Prognosis of Tuberculosis in Children. *Am. J. Med.*, 9:623, 1950.
15. Lincoln, E. M.: Indications for Treatment of Tuberculosis in Children. *Am. J. Surg.*, 89:634, 1955.
16. Lincoln, E. M., Sewell, E. M., and Anastasiades, A. A.: The Treatment of Primary Tuberculosis in Children. *Postgrad. Med.*, 16:422, 1954.
17. Meyer, M., Middlebrook, G., and Robinson, A.: The Treatment of Primary Tuberculosis in Infancy. *J. Pediat.*, 46:398, 1955.
18. Meyer, S.: Statistical Investigations of the Relationship of Tuberculosis Morbidity and Mortality to Infection. *Acta tuberc. Scandinav.*, supp. 19, 1949.
19. Miller, J. A., and Wallgren, A.: *Pulmonary Tuberculosis in Infants and Children*. New York, Thomas Nelson & Sons, 1939.
20. Opie, E. L., McPhedran, F. M., and Putnam, P.: The Fate of Persons in Contact with Tuberculosis. *Am. J. Hyg.*, 22:644, 1935.
21. Price, D. S.: *Tuberculosis in Childhood*. Bristol, England, John Wright and Sons, 1948.
22. Schmidt, L. H.: Some Observations on the Utility of Simian Pulmonary Tuberculosis in Defining the Therapeutic Potentialities of Isoniazid, in *Proceedings of the International Symposium on Tuberculosis in Infancy and Childhood*. To be published.
23. Shane, S. J., and Riley, C.: Tuberculous Meningitis: Combined Therapy with Cortisone and Antimicrobial Agents. *New England J. Med.*, 249:829, 1953.
24. Waring, J. J.: The Current Treatment of Pulmonary Tuberculosis. *Dis. of Chest*, 25:361, 1954.

550 First Avenue
New York 16, New York

TOXICOLOGY OF THE ANTIBIOTICS

B. M. KAGAN, M.D.

The most generally used antibiotics are penicillin, tetracycline, chlortetracycline, oxytetracycline, chloramphenicol, erythromycin and streptomycin. Most of the time their use is associated with no significant toxic effect. When they do occur, the toxic effects vary from mild to fatal. A higher incidence of toxic reactions follows the use of some antibiotics than of others.

The reactions may be allergic or anaphylactic; they may affect principally certain systems, e.g., gastrointestinal, nervous, hematologic or renal; they may be accidental; they may be due to overgrowth of nonsusceptible organisms, or to vitamin deficiency.

ALLERGIC REACTIONS

These reactions have been observed most often in subjects who have a personal or family history of allergy, e.g., hay fever or asthma. Some allergic reactions, however, occur in patients without such history. The allergic reactions most frequently seen are a "serum sickness"-like illness with urticaria, arthralgia and fever as the most prominent manifestations, angioneurotic edema, pruritus, asthma and exfoliative dermatitis. There may be an "incubation" period of five to 14 days.[1] The antibiotics which are primarily responsible for such reactions are penicillin, chlortetracycline, oxytetracycline, tetracycline and polymyxin B. However, most of the antibiotics have produced at least mild reactions in some sensitive patients. Antihistaminic agents decrease or prevent the minor reactions, but are relatively useless in preventing or minimizing the more severe ones. The minor reactions and, to a degree, the severe ones are usually favorably modified by cortisone or its derivatives, or ACTH.

From the Department of Pediatrics, School of Medicine, University of California at Los Angeles, and the Department of Pediatrics, Cedars of Lebanon Hospital, Los Angeles.

ANAPHYLACTIC REACTIONS

Anaphylactic reactions occur most frequently in persons who have shown previous sensitivity to the antibiotic, but a few have not had such a history. The reactions are characterized by sudden weakness, profuse sweating, difficulty in breathing, respiratory paralysis and circulatory collapse. They have been reported in a number of instances following intramuscular penicillin (death has resulted within 15 minutes after injection in some cases). One severe nonfatal case has been reported as a result of oral[10] administration of the drug, and six severe nonfatal cases as a result of topical administration.[3]

Penicillin has been responsible for most such reactions due to antibiotics. Persons who have shown previous sensitivity to this drug should be given a skin test (scratch, 10,000 units of crystalline penicillin G per milliliter in distilled water; the reaction should be read at 20 minutes; a positive reaction consists of a definite wheal and flare) prior to its administration. A negative skin test, however, does not give assurance that such a reaction will not occur.

Fortunately, serious anaphylactic reactions to penicillin are rare. However, it appears that more persons are attaining a high level of sensitization through repeated exposure to the drug.[3] Fifteen deaths were reported in an 18 month period during 1952–53.[7] Some have recommended that penicillin be given in the lower portion of the upper arm, so that a tourniquet can be applied easily and immediately if warranted.[7] It has been advised[1] that the first few drops of the preparation be injected, followed by a 45 second pause before the remainder of the dose is given. Epinephrine should be available whenever penicillin is to be injected. Oral use of the antibiotics is to be preferred whenever possible because both allergic and anaphylactic reactions appear to be less common when antibiotics are given by this route.

SYSTEMIC REACTIONS

Gastrointestinal

Gastrointestinal symptoms are common, especially following oral administration of antibiotics. The reactions vary from soreness of the oral mucosa and nausea to severe diarrhea. In most instances the reactions are mild and the drug may be continued without fear of further untoward effects. Sometimes the effects disappear while the drug is still being given. Mild taste disturbances often occur during the use of troches. Nausea caused by the administration of the tetracycline drugs (tetracycline, chlortetracycline and oxytetracycline) may often be avoided by the simultaneous administration of cold milk with each dose.

Diarrhea may be due to a change of intestinal flora. In these cases

administration of the antibiotic should be discontinued and appropriate drugs given to counteract the growth of newly developing bacteria or fungi. When diarrhea is due to the latter, oral administration of nystatin (Mycostatin) has been clinically effective. Pruritis ani may be disturbing. When it is due to overgrowth of fungi, nystatin again or the external application of gentian violet (methylrosaniline chloride) to the affected areas is often effective.

Neurotoxicity

Some of the antibiotics produce specific neurotoxic effects. Both streptomycin and dihydrostreptomycin may be toxic to the auditory division of the eighth cranial nerve. Streptomycin, however, is primarily toxic to the vestibular branch of the eighth nerve, while dihydrostreptomycin is responsible for most auditory damage. It has been suggested by some that if these drugs are used in equal proportions simultaneously, the incidence of such side effects is reduced. In general, the loss of hearing and impairment in vestibular function are irreversible. Fortunately, signs of toxicity are rarely seen until therapy has been given for three months or longer. These drugs are being used frequently in some areas for prophylaxis in premature infants. Long-term studies for their effect, particularly on hearing in these infants, are much needed.

A new derivative, streptomycin pantothenate, is reported by the Europeans to be free of these toxic effects.

Polmyxin B and other antibiotics are sometimes associated with neurotoxicity such as paresthesias which are transient.[5]

Blood Dyscrasias

The use of chloramphenicol has been associated with blood dyscrasias, including aplastic anemia, leukopenia, thrombocytopenic purpura, and granulocytopenia. However, as Lewis et al. have pointed out,[8] it cannot be stated categorically that the incidence of blood dyscrasia has increased since chloramphenicol became available. It is recommended[2, 6, 12] that if chloramphenicol is given, "frequent and careful blood examinations (twice weekly) be made and the drug discontinued with the first manifestation of depression of bone marrow activity." Streptomycin has also been reported to produce blood dyscrasias on rare occasions, only one fatal case having been reported.[3]

Renal Involvement

Renal involvement,[3] as manifested by elevated blood nonprotein nitrogen, urine albumin and abnormal phenolsulfonphthalein excretion,

may follow the use of streptomycin, polymyxin B, bacitracin or neomycin. The effects due to streptomycin and polymyxin B are usually transient, but those due to bacitracin and neomycin may be persistent and serious. Renal toxic effects due to polymyxin B have been exaggerated because the early reports were based upon experience with a different derivative, i.e., polymyxin D.[5] All these antibiotics should be used with caution in the presence of renal disease.

Liver Involvement

When liver damage occurs, it is fortunately transient in most cases. It is manifested primarily by temporary hyperbilirubinemia and symptoms similar to those seen in intrahepatic obstructive jaundice. The antibiotic primarily responsible is chlortetracycline, while streptomycin also may occasionally be involved.

OTHER REACTIONS

Accidental Reactions

Accidental intravenous administration of an intramuscular preparation of penicillin may give an immediate serious or fatal reaction. The patient becomes lethargic, may salivate excessively and have rapid respiration and heart rate. Some of the "anaphylactic" reactions may in fact be due to such accidents. Animal experiments have shown that intravenous administration of an intramuscular preparation of penicillin can be fatal.[4] The incidence can be reduced if a sufficiently large needle is used and the plunger withdrawn before injection to be certain the needle is not in a blood vessel.

Overgrowth of Nonsusceptible Organisms

Many of the organisms normally inhabiting the gastrointestinal tract are harmless in the concentrations in which they exist. Since each is competing for survival, the numbers of each species are kept relatively constant. However, if some of the susceptible bacteria are removed from the environment by an antibiotic, a nonsusceptible organism (e.g., *Candida albicans* in the case of the tetracyclines) may flourish and can cause serious damage. The incidence of well authenticated cases of fatalities due to overgrowth of fungi is low.[3] Recently, overgrowth of resistant staphylococci and *Streptococcus faecalis* in the gastrointestinal tract has been particularly distressing, and fatal in a few cases.[11] Unless specifically requested in stool cultures, their presence may be overlooked.

Overgrowth of gram-negative organisms may occur when an anti-

biotic is used which is primarily active against the gram-positive organisms, e.g., penicillin. The emergence of such microorganisms as type-specific *Escherichia coli* or *Pseudomonas aeruginosa* can give rise to severe gastrointestinal involvement. Oral neomycin has been particularly effective in type-specific *E. coli* enteric infections, and oral polymyxin B has proved effective in eliminating *Pseudomonas aeruginosa* when it is present in the gastrointestinal tract.[9]

A more insidious type of overgrowth, which may result in an aggravation of the initial infection, occurs when a resistant strain of a previously susceptible organism develops during treatment. This occurs especially during prolonged therapy, as, for example, in tuberculosis.

Appropriate therapy in most cases can be instituted after identification of the overgrowing organism and determination of its sensitivity to antibiotics. Nystatin (Mycostatin) is often clinically effective against monilial overgrowth in the gastrointestinal tract.

VITAMIN DEFICIENCY RESULTING FROM ANTIBIOTIC THERAPY

There are at least three different mechanisms by which a vitamin deficiency can result from antibiotic therapy.

Vitamin K and various members of the B complex group are normally synthesized by the bacteria which constitute the normal intestinal flora. The broad-spectrum antibiotics can eliminate large numbers of these and thus indirectly cause frank vitamin K and B complex deficiencies.

Appetite and digestion are often disturbed not only by the infectious process itself, but also particularly by chlortetracycline and oxytetracycline. This may result in reduced food consumption and concomitant vitamin deficiency.

An even more complicated situation arises when diarrhea or vomiting follows use of the antibiotics.

Administration of vitamin supplements has been recommended to counteract these effects.

MISCELLANEOUS REACTIONS

Mild local pain and tenderness frequently follow intramuscular injections of the antibiotics. Many of the earlier intramuscular penicillin preparations resulted in sterile abscesses and/or pain at the site of injection. Many of these effects were due to impurities, which have been largely eliminated. Some, however, may still produce some local pain which may persist for several days. Local pain can usually be avoided by deep intramuscular injection. Venous irritation and thrombosis may follow intravenous injection. Fever may be caused by any

of the antibiotics, and this cause should be considered whenever fever persists without other obvious cause. The Jarisch-Herxheimer reaction, usually characterized by fever and rarely by a cutaneous flare of secondary lesions of syphilis, has been observed in a few isolated cases when penicillin or chlortetracycline was used in the treatment of syphilis. Death has been caused by intrathecal administration of large doses of water-soluble penicillin. This may have been due to direct chemical action on the nervous system.

Contact sensitivity following topical application of antibiotics may occur. Such reactions are rarely troublesome and are usually relieved by withdrawing the drug.

CONCLUDING REMARKS

In general, infants and children have fewer reactions than do adults. There are also age differences in susceptibility to superinfection (for example, the susceptibility of newborn and premature infants to gram-negative infections, especially *E. coli*, and their increased occurrence when penicillin is used alone).

In view of the effectiveness of the antibiotics, the low incidence and general mildness of untoward reactions from them place them among the most remarkable of all the therapeutic achievements. The fact, however, that a certain calculated risk must be assumed in their use makes it mandatory that the indications be carefully considered and that they should not be used when simple remedies or no therapy at all would be just as effective or even more effective.

REFERENCES

1. Boger, W. P., and others: Allergic Reactions to Penicillin: A Panel Discussion. *J. Allergy*, 24:383, 1953.
2. Claudon, D. B., and Hollbrook, A. A.: Fatal Aplastic Anemia Associated with Chloramphenicol (Chloromycetin) Therapy. *J.A.M.A.*, 149:912, 1952.
3. Kagan, B. M., and Faller, L.: Untoward Reactions to Antibiotics. *M. Clin. North America*, 39:111, 1955.
4. Kagan, B. M., Nierenberg, M., Goldberg, D., and Milzer, A.: Studies of Penicillin in Pediatrics. III. Procaine Penicillin G. in Sesame Oil, in Peanut Oil with 2% Aluminum Monostearate and in Water with Sodium Carboxymethylcellulose. *Pediatrics*, 5:664, 1950.
5. Kagan, B. M., Krevsky, D., Milzer, A., and Locke, M.: Polymyxin B and Polymyxin E. Clinical and Laboratory Studies. *J. Lab. & Clin. Med.*, 37:402, 1951.
6. Karelitz, S.: Choice of an Antibiotic: An Interpretative Review. *J. Pediat.*, 42: 478, 1953.
7. Kern, A. R., and Wimberley, N. A., Jr.: Penicillin Reactions; Their Nature, Growing Importance, Recognition, Management and Prevention. *Am. J. M. Sc.*, 226:357, 1953.
8. Lewis, C. N., and others: Chloramphenicol (Chloromycetin) in Relation to Blood Dyscrasias, with Observations on Other Drugs. *Antibiotics & Chemother.*, 2:601, 1952.

9. Mills, G. Y., and Kagan, B. M.: Effect of Oral Polymyxin B on Pseudomonas Aeruginosa in the Gastrointestinal Tract. *Ann. Int. Med.*, 40:26, 1954.
10. Pierce, H. E.: An Anaphylactoid Reaction Due to Oral Penicillin: A Case Report. *J. Nat. M. A.*, 45:68, 1953.
11. Smith, D. T.: The Disturbance of the Normal Bacterial Ecology by the Administration of Antibiotics with the Development of New Clinical Syndromes. *Ann. Int. Med.*, 37:1135, 1952.
12. Sturgeon, P.: Fatal Aplastic Anemia in Children Following Chloramphenicol (Chloromycetin) Therapy. *J.A.M.A.*, 149:918, 1952.

4833 Fountain Avenue
Los Angeles 29, California

PEDIATRIC DOSAGES AND ROUTES OF ADMINISTRATION OF ANTIBIOTICS

ERWIN NETER, M.D.

DAVID T. KARZON, M.D.

The present success of antibiotic therapy and prophylaxis of a large variety of infectious diseases is of such a magnitude that we can consider it at least a partial fulfillment of Ehrlich's dreams of a half century ago. However, even the least toxic of the currently available antibiotics is not entirely free from side effects, and it is for this reason, among others, that antibiotics should be used only when indicated.

Antibiotics and chemotherapeutic agents undoubtedly are used more extensively in pediatric than in adult practice. The following characteristics of childhood infections appear to justify this widespread use: (1) rapidity of progression of acute infections in infancy and early childhood; (2) increased susceptibility to invasive bacterial infection, especially in the newborn and young infant; (3) the high incidence of secondary bacterial infection following upper respiratory disease of nonbacterial etiology; and (4) the subtle nature of some of the characteristic symptoms and signs of infection in infants and young children. Additionally, the sulfonamides and antibiotics are generally well tolerated by children. For example, drug sensitivity is less of a problem in children than in adults. Nonetheless, the indiscriminate use of chemotherapeutic agents cannot be condoned and does not substitute for competent examination and evaluation of the child's illness. Certain basic aspects of antibiotic management may be briefly stated prior to the discussion of the dosages and routes of administration of various antibiotics in pediatric practice.

CHOICE OF ANTIBIOTIC

At present we do not have available a truly broad-spectrum antibiotic which is effective in all infections. The clinician, therefore, has to select an antibiotic from a relatively large number of drugs. This selection is rendered more complex, since a number of antibiotics, even in identical dosage forms, are available commercially under numerous names. Whenever the physician is dealing with an important or potentially dangerous infection, an etiologic diagnosis should be made, if at all possible. On the basis of such a diagnosis the most effective antibiotic usually can be selected without further investigation.

There are certain pathogenic microorganisms whose susceptibility to various antibiotics does not vary materially from strain to strain. To this group, which may be termed *predictable*, belong such microorganisms as group A hemolytic streptococci, pneumococci, and the spirochete of syphilis, which cause infections that are always sensitive to certain antibiotics, particularly penicillin. On the other hand, there is a group of bacteria whose susceptibility varies substantially from strain to strain. This group may be termed *unpredictable*. Most notable among these latter microorganisms are the staphylococci and many gram-negative bacilli. Therefore in infections caused by these unpredictable etiologic agents it is often helpful to obtain information on the approximate sensitivity in vitro of the particular strain. However, even the best sensitivity test in vitro is no substitute for continued, thorough clinical evaluation of the patient, and even without sensitivity studies in vitro an intelligent first estimate of the probable therapeutic efficacy of a given antibiotic may be surmised from knowledge of past experience.

DOSAGES

The dosages of antibiotics used in various diseases depend upon numerous factors, including the toxicity, absorption, diffusion and excretion of the drug, the route of administration, the susceptibility of the etiologic agent and the nature and localization of the disease process. With almost entirely nontoxic drugs, such as penicillin, the dosage range may be enormous, from as little as 100,000 units to as much as 100,000,000 units a day. With more toxic drugs the range is relatively narrow. Certain antibiotics are readily absorbed from the gastrointestinal tract, whereas others are not (Table 16). For this reason large doses of potentially toxic but nonabsorbed drugs, such as bacitracin, polymyxin and neomycin, are well tolerated orally but not systemically. The need for larger doses of antibiotics over a prolonged period of time may be necessitated by certain localizations of the infectious process, for example, osteomyelitis and pneumococcal

meningitis. Similarly, a pneumococcal pharyngitis responds to therapy much more readily than acute purulent otitis media or meningitis caused by the identical strain.

It should be kept in mind, also, that an ordinary well tolerated dose of a given antibiotic may cause toxic effects in a patient who does not excrete the drug normally. All the common antibiotics and chemotherapeutic agents used systemically are excreted to a greater or less extent by the kidneys. Therefore situations which reduce renal excretion may effect unexpectedly high blood levels. Renal disease, shock and dehydration are common accompaniments of the severe forms of acute infection, and these states impair renal excretory function. Under these conditions the recommended dose of an antibiotic should be proportionately reduced. The rate of multiplication of pathogenic microorganisms also has a bearing on dosage and length of antibiotic treatment.

TABLE 16. *Gastrointestinal Absorption of Antibiotics after Oral Administration*

ABSORBED	NONABSORBED
Penicillin	Streptomycin
Tetracyclines	Neomycin
Chloramphenicol	Polymyxin B
Erythromycin	Bacitracin

For example, in tuberculosis, in which the organism has a relatively slow growth cycle, administration of streptomycin at infrequent intervals (12 to 48 hours) is efficacious.

Thought should be given to the cost of the available antibiotics and chemotherapeutic agents, provided they are of equal efficacy and freedom from toxicity. Patient acceptance should also be considered when deciding upon a given antibiotic and its route of administration.

Calculation of the dosage of antimicrobial agents used in pediatric practice is generally based upon the patient's weight. Because of the role of the kidneys in the excretion of such agents, the surface area may be a better basis for calculation of dosage for premature and newborn infants and may give better control of blood levels. The effect of the physiologically reduced renal function in premature and young infants upon antibiotic excretion and blood levels is not well documented.

When particularly high blood levels of penicillin are required, Benemid or carinamide, which interfere with the renal excretion of this antibiotic, may be administered simultaneously. Since these drugs may also interfere with the excretion of other antibiotics, such as bacitracin, caution must be exercised in order to avoid toxic blood levels.

ROUTES OF ADMINISTRATION

Whenever oral medication is feasible and effective, this route is preferred. With persistent vomiting or in patients with impaired consciousness the initial therapy will often be, of necessity, by the parenteral route or by gavage. The parenteral forms of the sulfonamides in appropriate dilution may be given safely by the subcutaneous route. Most antibiotics are better tolerated by intramuscular than subcutaneous injection, and with some of them, such as oxytetracycline and erythromycin, the subcutaneous injection may result in tissue damage. Therefore care must be taken that these drugs are injected into the muscle. In the choice of the route of administration one must also anticipate the length of treatment. For example, in the protracted treatment of pneumococcal meningitis or staphylococcal osteomyelitis in an infant it may be wiser to begin with intravenous rather than intramuscular administration of the large doses of penicillin required. Thus the problem of sparing adequate areas for intramuscular injection later in the course of the disease is anticipated. Also, one must keep in mind that in conditions with poor peripheral circulation subcutaneously injected drugs may be poorly absorbed.

COMBINED ANTIBIOTIC THERAPY

Simultaneous use of two or more antibiotics is indicated in mixed infections in which all the etiologically important microorganisms are not optimally susceptible to a single antibiotic. Such a regimen is also of great value when two or more antibiotics act synergistically and thus produce antimicrobial effects superior to those made possible by either alone (Table 17). For example, penicillin and streptomycin act synergistically, and this combination is now the treatment of choice in certain cases of subacute bacterial endocarditis. Combinations of drugs may also be effective in avoiding the development of drug-resistant microorganisms, as in the use of streptomycin, isoniazid and para-aminosalicylic acid in tuberculosis. Finally, combined therapy may be a necessity for a limited time in patients with a bacterial infection of undetermined etiology. For example, several antibacterial agents may have to be used in young children with meningitis (for example, sulfadiazine, chloramphenicol and penicillin) until the etiologic diagnosis has been established. Then the inappropriate drugs should be discontinued. The phenomenon of antibiotic antagonism (drugs of group B antagonizing those of group A—see Table 17), which can be demonstrated under special conditions in vitro and in experimental animals, does not usually apply to clinical pediatric situations. The exception to this rule may be the simultaneous use of penicillin and a bacteriostatic antibiotic in pneumococcal meningitis, in which large

TABLE 17. *Synergistic Combinations of Antibiotics (after Jawetz[2])*

GROUP A BACTERICIDAL	GROUP B BACTERIOSTATIC
Penicillin	Tetracycline
Streptomycin	Chlortetracycline
Bacitracin	Oxytetracycline
Neomycin	Chloramphenicol
Polymyxin B	Erythromycin

Synergistic: Drugs of group A in combination; occasionally, drugs of groups A and B in combination.
Not synergistic: Drugs of group B in combination.

doses of penicillin apparently are more effective than penicillin in like amounts used in conjunction with a tetracycline.[5]

FAILURE OF ANTIBIOTIC THERAPY

In view of the fact that failure of antibiotic treatment may be due to superinfection, for example, by staphylococcus, various gram-negative bacilli and Candida (Monilia), it cannot be too strongly stressed that under these circumstances a complete clinical and laboratory re-evaluation of the patient is of the utmost importance. Only then is the physician in a position to decide intelligently which change, if any, should be made in chemotherapy.

PROPHYLAXIS

The prevention of infectious diseases usually can be accomplished successfully with doses of antibiotics and other chemotherapeutic agents which fail to eradicate an established infection. To illustrate, 200,000 units of penicillin per day or even less prevent infection with group A hemolytic streptococci, but may fail to eradicate the etiologic agent in a patient with active streptococcal infection.

SULFONAMIDES

It may be pointed out that even in this antibiotic era there is still a place in pediatrics for sulfonamides, particularly in acute infections of the urinary tract, bacillary dysentery (shigellosis), upper respiratory infections of bacterial origin and meningococcal meningitis. Sulfonamides are also useful as a supplement to penicillin therapy in certain infections.

RESEARCH

The search for new and better antibiotics continues, and it can be confidently expected that this research effort will make available new antibiotics to the practicing physician in the near future. For example,

TABLE 18. *Therapeutic Dosages and Routes of Administration of Antibiotics and Chemotherapeutic Agents in Pediatric Practice*

ANTIMICROBIAL AGENTS	SELECTED TRADE NAMES	ROUTES	MOST INFECTIONS		SPECIAL OR SEVERE INFECTIONS	
			Dosages	Intervals	Dosages	Intervals
Penicillin: Crystalline penicillin G or O (aqueous)	Numerous	IM or IV	20,000–50,000 U/kg./24 hrs. 300,000–600,000 U/24 hrs. in older children	4–6 hrs. or continuous IV	1–50 million U/24 hrs.	2–3 hrs. or continuous IV
		Ith			5000–10,000 U (1000 U/ml.)	24 hrs.
Oral penicillin (G or V)	Numerous	Oral	2–4 times the IM dose	4–8 hrs.	Prophylaxis of rheumatic fever: 200,000–400,000 U/24 hrs.	24 hrs.
Procaine penicillin G (or O)	Numerous	IM	Same as crystalline penicillin, aqueous	24 hrs.	Same as crystalline penicillin (aqueous)	12 hrs.
Benzathine penicillin G	Bicillin, Duapen, Permapen, etc.	Oral	300,000–1.2 million U/24 hrs.	4–8 hrs.	Prophylaxis of rheumatic fever: 200,000–400,000 U/24 hrs.	24 hrs.
		IM	600,000–1.2 million U/24 hrs.	24–72 hrs.	Prophylaxis of rheumatic fever: 1.2 million units	Monthly
Combinations of above injectible penicillins	Numerous	IM	600,000–1.2 million U/24 hrs.	24–72 hrs.		
Streptomycin, dihydrostreptomycin, alone or in equal mixture	Numerous	Oral	40–100 mg./kg./24 hrs. (For enteric infections only)	4–6 hrs.		
		IM	20–40 mg./kg./24 hrs.	8–24 hrs.	(In tuberculosis, streptomycin used in conjunction with isoniazid and PAS)	
		Ith			20–50 mg. (10 mg./ml.) of streptomycin	1–2 days
Tetracyclines: Chlortetracycline	Aureomycin	Oral	12.5–25 mg./kg./24 hrs.	6 (4–8) hrs.	25–40 mg./kg./24 hrs.	6 (4–8) hrs.
		IV			12.5–25 mg./kg./24 hrs. (Maximum adult dose 2 gm./24 hrs.)	6–12 hrs.
Oxytetracycline	Terramycin	Oral	20–30 mg./kg./24 hrs.	6 (4–8) hrs.	30–40 mg./kg./24 hrs.	6 hrs.
		IM			5–10 mg./kg./24 hrs. (Maximum adult dose 400 mg./24 hrs.)	8 hrs.
		IV			10–20 mg./kg./24 hrs. (Maximum adult dose 2 gm./24 hrs.)	6–12 hrs.

Duplicate copies of Tables 18 and 19 will be found at the back of the book for removal and reference.

TABLE 18. *Therapeutic Dosages and Routes of Administration of Antibiotics and Chemotherapeutic Agents in Pediatric Practice (Continued)*

ANTIMICROBIAL AGENTS	SELECTED TRADE NAMES	ROUTES	MOST INFECTIONS		SPECIAL OR SEVERE INFECTIONS	
			Dosages	Intervals	Dosages	Intervals
Tetracycline	Achromycin, Panmycin, Polycycline, Steclin, Tetracyn	Oral	20–30 mg./kg./24 hrs.	6 (4–8) hrs.	30–40 mg./kg./24 hrs.	6 (4–8) hrs.
		IM			3–10 mg./kg./24 hrs. (Maximum adult dose 400–600 mg./24 hrs.)	8–12 hrs.
		IV			12.5–25 mg./kg./24 hrs. (Maximum adult dose 2 gm./24 hrs.)	6–12 hrs.
Chloramphenicol	Chloromycetin	Oral	30–50 mg./kg./24 hrs.	6 (4–8) hrs.	75–100 mg./kg./24 hrs.	4–6 hrs.
		IM			100–150 mg./kg./24 hrs. (children up to 15 kg.)	8–12 hrs.
					1–2 gm. 24 hrs. (children over 15 kg.)	12 hrs.
		IV			60–80 mg./kg./24 hrs. (Maximum adult dose 4 gm./24 hrs.	6–8 hrs.
Erythromycin	Erythrocin, Ilotycin	Oral	20–40 mg. kg. 24 hrs. (Maximum adult dose 1–2 gm./24 hrs.)	6 hrs.	50 mg./kg./24 hrs.	6 hrs.
		IM			10 mg./kg./24 hrs.	8–12 hrs.
		IV			25–40 mg./kg./24 hrs.	6–8 hrs.
Carbomycin	Magnamycin	Oral	50–100 mg./kg./24 hrs.	6 hrs.		
Polymyxin B (1 mg. = 10,000 U)	Aerosporin	Oral	10–20 mg./kg. 24 hrs. (for enteric infections only)	6–8 hrs.		
		IM			1.5–2.5 mg./kg./24 hrs. (maximum 200 mg./24 hrs.) (preferably for less than 6–10 days)	6–8 hrs.
		Ith			2 mg. for infants under 2 yrs.	24–48 hrs.
					5 mg. for children over 2 yrs. (1 mg./ml.)	24–48 hrs.
		Topical	1–2.5 mg./ml. or gm.			
Bacitracin (1 mg. = 50 U)		Oral	100–400 U/kg. 24 hrs. (for enteric infections only)	4–6 hrs.		
		IM			600–1200 U/kg./24 hrs. (Maximum adult dose 100,000 U/24 hrs.)	6–8 hrs.

TABLE 18. *Therapeutic Dosages and Routes of Administration of Antibiotics and Chemotherapeutic Agents in Pediatric Practice (Continued)*

ANTIMICROBIAL AGENTS	SELECTED TRADE NAMES	ROUTES	MOST INFECTIONS		SPECIAL OR SEVERE INFECTIONS	
			Dosages	Intervals	Dosages	Intervals
Bacitracin (cont'd.)		Ith			500–2000 U (for infants under 2 yrs.)	12–24 hrs.
					2000–10,000 U (for children over 2 yrs.) 500–1000 U/ml.	12–24 hrs.
		Topical	500 U (100–1000 U) /ml. or gm.	12–24 hrs.		
Neomycin sulfate	Mycifradin	Oral	50–100 mg./kg./24 hrs. (for enteric infections only)	4–6 hrs.		
		IM			10–15 mg./kg./24 hrs. (maximum 1 gm.)	6 hrs. (up to 10 days)
		Topical	5 mg./gm. or ml.	12–24 hrs.		
Tyrothrycin		Topical	0.25–0.5 mg./gm. or ml.			
Viomycin	Viocin	IM			(Used in selected cases of tuberculosis only)	
Nystatin	Mycostatin	Oral	(400,000–800,000 U/24 hrs. for infants, 1–2 million U/24 hrs. for older children)	6–8 hrs.		
		Topical	100,000 U/gm.			
Sulfonamides	Numerous	Oral	100–200 mg./kg./24 hrs.	4–6 hrs.		
Sulfadiazine, Sulfamerazine, Sulfisoxazole		SC or IM			50–100 mg./kg./24 hrs. (parenteral SC or IM preparations only)	8 hrs.
		IV			50 mg./kg. stat (intravenous preparations only)	6–8 hrs.
Nitrofurantoin	Furadantin	Oral	5–10 mg./kg. 24 hrs.	6 hrs.		

IM: intramuscular; IV: intravenous; Ith: intrathecal; SC: subcutaneous; U: units.

penicillin V, made commercially available recently, may prove to be useful. The value of several new antibiotics, such as synnematin B, streptonivicin (Albamycin), cathomycin and spiramycin is under study at the present time.

SUMMARY OF DOSAGES AND ROUTES OF ADMINISTRATION

Table 18 summarizes present data on the usual dosages of the clinically available antibiotics and sulfonamides, and Table 19 presents

TABLE 19. *Commercially Available Antibiotic Preparations*

ANTIBIOTICS	ROUTES OF ADMINISTRATION								
	Oral		Injection		Topical				
	Tablets Capsules	Solutions Suspensions	IM	IV	Powder Solutions Ointments	Troches	Preparations: Ear	Eye	Vaginal
Single Drugs									
Crystalline penicillin	+	+	+	+	+	−	−	+	+
Procaine penicillin	+	+	+	−	+	+	−	+	−
Benzathine penicillin	+	+	+	−	−	−	−	−	−
Streptomycin and dihydrostreptomycin	−	+	+	−	+	−	+	−	−
Chlortetracycline	+	+	−	+	+	+	+	+	+
Oxytetracycline	+	+	+	+	+	+	+	+	+
Tetracycline	+	+	+	+	+	+	+	+	−
Chloramphenicol	+	+	+	+	+	−	+	+	−
Erythromycin	+	+	+	+	+	−	+	+	−
Carbomycin	+	−	−	−	−	−	−	−	−
Polymyxin B	+	+	+	−	+	−	+	+	−
Bacitracin	+	−	+	+	+	+	−	+	+
Neomycin	+	+	+	−	+	−	+	+	−
Tyrothricin	−	−	−	−	+	+	+	−	−
Viomycin	−	−	+	−	−	−	−	−	−
Nystatin	+	−	−	−	+	−	−	−	+
Sulfonamides	+	+	+	+	+	+	+	+	+
Nitrofurantoin	+	+	−	−	−	−	−	−	−
Drugs in Combination									
Aqueous and procaine penicillin	−	−	+	−	−	−	−	−	−
Procaine and benzathine penicillin	−	−	+	−	−	−	−	−	−
Aqueous, procaine and benzathine penicillin	−	−	+	−	−	−	−	−	−
Penicillin and sulfonamides	+	+	−	−	−	−	−	−	−
Penicillin and streptomycin	−	−	+	−	+	+	−	−	+
Penicillin and bacitracin	−	−	−	−	+	+	−	+	−
Tetracycline and nystatin	+	−	−	−	−	−	−	−	−
Tetracycline and sulfonamide	−	+	−	−	−	−	−	−	−
Erythromycin and sulfonamide	−	+	−	−	−	−	−	−	−
Bacitracin and neomycin	+	−	−	−	+	+	−	−	−
Bacitracin, neomycin and tyrothricin	−	−	−	−	−	+	−	−	−
Bacitricin, neomycin and polymyxin	+	−	−	−	+	+	−	+	−
Bacitracin and polymyxin	+	−	−	−	+	+	−	+	−
Bacitracin and tyrothricin	−	−	−	−	+	+	−	−	−
Neomycin and erythromycin	−	−	−	−	+	−	−	−	−
Neomycin and gramicidin*	−	−	−	−	+	+	−	−	−
Neomycin, gramicidin* and polymyxin	−	−	−	−	−	−	−	+	−
Penicillin, streptomycin and bacitracin	−	−	−	−	+	−	−	−	−
Oxytetracycline and polymyxin	−	−	−	−	+	−	+	+	+
Polymyxin and sulfonamides	+	+	−	−	−	−	−	−	−
Streptomycin, bacitracin and polymyxin	+	−	−	−	+	−	−	−	−

+: available (1955); −: not available (1955); *: active portion of Tyrothricin.

a list of these drugs, alone and in various combinations, available for a variety of routes of administration. For the sake of uniformity the doses are expressed throughout in milligrams or units per kilogram of body weight. It must be stressed that neither of the tables is complete, that dosages given are averages, that recommended doses of some of the antibiotics may be changed in the future, and that antibiotic management, including dosage and route of administration, must be planned for the individual patient.

The authors wish to express their sincerest thanks to the many experts in the field, associated with universities, hospitals and pharmaceutical houses, who reviewed Tables 18 and 19 and contributed valuable suggestions.

REFERENCES

1. American Academy of Pediatrics: Report of the Committee on the Control of Infectious Diseases. American Academy of Pediatrics, 1955.
2. Flippin, H. F., and Eisenberg, G. M.: *Antimicrobial Therapy in Medical Practice*. Philadelphia, F. A. Davis Company, 1955.
3. Jawetz, E., Gunnison, J. B., Coleman, V. R., and Kempe, C. H.: A Laboratory Test for Bacterial Sensitivity to Combinations of Antibiotics. *Am. J. Clin. Path.*, 25:1016, 1955.
4. Kempe, C. H.: The Use of Antibacterial Agents. *Pediatrics*, 15:221, 1955.
5. Lepper, M. H., and Dowling, H. F.: The Treatment of Pneumococcic Meningitis with Penicillin Alone Compared with Penicillin Plus Aureomycin, Including Observations on an Apparent Antagonism between Penicillin and Aureomycin. *Arch. Int. Med.*, 88:489, 1951.
6. Robbins, F. C., and Eiben, R. M.: Specific Treatment of Infectious Diseases. PEDIAT. CLIN. NORTH AMERICA, 1:405, 1954.
7. Ross, S.: Antibiotic Therapy in Pediatrics, in Welch, H.: *Principles and Practice of Antibiotic Therapy*. New York, Medical Encyclopedia, Inc., 1954.
8. Welch, H., and Lewis, C. N.: Antibiotic Therapy. New York, Medical Encyclopedia, Inc., 1953.

Children's Hospital
Buffalo 22, New York

POLIOMYELITIS, 1956

The Changing Picture in the United States with Salk Vaccine

HART E. VAN RIPER, M.D.

The goal of control of paralytic poliomyelitis is now clearly in sight. It depends largely upon the continued cooperation of physicians in administering poliomyelitis vaccine to as many children and adults as possible as soon as possible. The brunt of this task, today and in the future, falls upon the pediatrician and the general practitioner.

The situation in 1956 is special—akin to a medical emergency—since it is complicated by the magnitude of the problem and by some uncertainty about vaccine supply. Beginning immediately, and certainly in the long future, vaccination against paralytic poliomyelitis should be a routine and standard prophylactic practice in pediatrics.

Ideally, vaccination against paralytic poliomyelitis should begin some time in the second six months of life. The newborn infant generally has a high degree of protection from maternal antibodies for about six months. The time is, of course, somewhat variable in individual cases; but, in general, the protective effect, as judged by clinical experience and antibody titer examinations, prevails for about six months.

Poliomyelitis vaccination under six months of age is probably inadvisable; first, because the maternal antibody protection largely prevails; and secondly, because the capacity to produce poliomyelitis antibodies is not so great during the first six months of life as in later months and years. However, there is no reason to believe that administration of poliomyelitis vaccine before six months of age would be harmful.

From the National Foundation for Infantile Paralysis, New York City.

The ideal dosage schedule, with the Salk poliomyelitis vaccine as presently constituted, is two 1-cc. doses intramuscularly spaced anywhere from two to six weeks apart, followed by a booster injection of 1 cc. given at least seven months to one year later.

The first two inoculations can be timed to coincide with any convenient schedule of appointments and other vaccinations and inoculations commonly given in pediatric practice. There is no contraindication to giving Salk vaccine along with any of the standard immunizing agents against diphtheria, pertussis, tetanus or any other disease Because of the processing problems involved it seems unlikely, however, —at least for some time to come—that the poliomyelitis vaccine will be included in the same vial with other immunizing agents.

One injection is actually sufficient to give primary immunization or "take" of the Salk poliomyelitis vaccine. However, experience with vaccines of the potency used in 1955 indicated that the vaccine did not "take" on the first inoculation in about one in five children inoculated. At least no measurable increase in antibody titer was recorded. However, in a high percentage of the children whose vaccination did not "take" on the first inoculation, primary sensitization was obtained on the second inoculation.

The second inoculation, spaced two to six weeks after the first, may be considered an "insurance" inoculation. It will provide primary sensitization for those in whom the first shot failed to take. It will also provide a slight increase in antibody titer. With improved vaccines it is probable that the percentage of "takes" with one inoculation will be pushed higher than 80 per cent. It is cheaper and simpler to give a second inoculation than to test for the presence of poliomyelitis antibodies in the blood following the first inoculation.

We have no easy, inexpensive test on the order of the Schick test for determining whether or not a person has had poliomyelitis. Several investigators are interested in and working on possible "skin tests" for the diagnosis and detection of poliomyelitis infection. How soon such tests will actually be developed to a point of practical usefulness, if they can be developed at all, is not known.

However, there is available a time-consuming and rather expensive test for determining past poliomyelitis infection: the neutralization test, performed in tissue culture. This test takes about a week. Blood samples must be tested against all three types of poliomyelitis virus separately.

The complement-fixation test is less expensive and less time-consuming, but has not yet been studied sufficiently to assure reasonably reliable findings.

EFFECTIVENESS OF SALK POLIOMYELITIS VACCINE WITH RESPECT TO AGE

Most of the accumulated and published evidence on the safety and effectiveness of the Salk poliomyelitis vaccine has related to children in the six to 10 year age group. Since this is the age group most susceptible, statistically speaking, to attack of paralytic poliomyelitis, the use of vaccine supplies available in 1954 and 1955 was largely concentrated in this age group. The few studies that have been made on the question of vaccine effectiveness at different age levels show convincingly that in terms of antibody response to the Salk vaccine, age (above six months) makes little difference. Salk himself studied antibody response to vaccine against poliovirus types 1, 2 and 3 in a group of 19 children aged two through five years, who had received two 1-cc. doses four weeks apart. He found no significant difference in antibody response in these children from that observed in 24 subjects aged six through 18 years who received the same dosage of vaccine or from type 1 antibody response among 87 subjects, aged one to 10 plus years, in whom paralytic poliomyelitis had produced a so-called natural immunity.

Brown[1] and others[1, 2] at the University of Michigan have followed up a series of infants who were aged two to 12 months when first inoculations with poliomyelitis vaccine were made in 1954. In these infants they found a satisfactory response to primary vaccination, followed by a gradual decline and an excellent response to booster inoculation.

"BOOSTER" INOCULATIONS

The value of the properly timed first "booster" inoculation of Salk vaccine *following primary sensitization* has been amply demonstrated. The timing of this booster is extremely important; it should not be given until at least seven months have elapsed since the primary "take," but it can be delayed for at least 12 months without lessening its effect. The delayed booster raises the antibody titer in sensitized subjects to levels equal to or higher than those obtained from naturally acquired infection. The observed decline of antibody titer from this high and presumably protective level is relatively slow, so far as it has yet been possible to observe.

Two of the most important unsolved clinical questions relating to the Salk vaccine remain that of how long the booster effect lasts and, conversely, how often second or third booster shots may be required to maintain relatively high immunity to paralytic poliomyelitis. It will take years before these questions are fully resolved. Research on it is continuing.

Though only future research can definitely answer the question, the chances are that the dosage schedule now recommended—two 1-cc.

doses, intramuscularly, spaced two to six weeks apart with a booster dose at least seven months later—will produce a fairly long-lasting immunity. This improved dosage schedule, first recommended by Salk in April, 1955, has never been put to full-scale epidemiologic and statistical test. The statistical demonstrations of effectiveness of the Salk vaccine have been made with dosage schedules far under the optimum —in most cases a single injection of vaccine.

Salk has observed a comparatively high level of antibody persisting in children who received their first inoculations of then-experimental vaccine nearly three years ago.

Brown's continuing studies on the effect of subsequent booster inoculations on the serologic status of 119 Michigan children first receiving poliomyelitis vaccine during the 1954 Poliomyelitis Vaccine Field Trial have also shown encouraging results. A good primary response to vaccination was followed by a gradual decline in antibody response over a period of 12 months to a point slightly higher than that observed before vaccination.

When a booster shot was given at this time, the effect was pronounced. The titers following the boosters in all children against all three types of poliovirus were much higher than before vaccination. In many subjects the increase in antibody titer was from less than 4 to more than 1024.

It will probably not turn out to be necessary to give booster doses of Salk vaccine annually.

THE 1956 EMERGENCY SITUATION

A compromise may sometimes have to be made between the ideal dosage schedule recommended for the Salk vaccine and the real situation with regard to vaccine supply in 1956.

Approximately 30,000,000 cc. of Salk vaccine were released in 1955. On the basis of reports from manufacturers and the Surgeon-General of the U.S. Public Health Service concerning estimated vaccine production, there is reason to believe that perhaps 70 million cc. may be available for distribution during the first six months of the year 1956. How much of this will get in the hands of private physicians is variable, depending upon decisions of state and local health authorities and their advisory committees.

If 70 million cc. become available, it would be about enough to provide a high degree of protection against paralytic poliomyelitis before the 1956 poliomyelitis season to all children in the most susceptible age groups (six months through 14 years) and pregnant women who request it. In round numbers, there are approximately 50 million persons in these categories. Probably 15 million children had received

one or more injections of Salk vaccine before March 1, 1955. This left about 35 million children and women to be vaccinated on an emergency basis before the 1956 season.

Granting rapid and equitable distribution and no unanticipated delays in processing and releasing vaccine (which requires a minimum of 120 days), we should have just about enough vaccine to give *two injections* each to 35 million people.

The following compromise or emergency dosage schedule of Salk vaccine coming into the physician's private practice therefore seems warranted:

1. Do not give "booster" shots between now and July 1. There is minimal risk if, in fact, any at all, in giving primary or booster shots *during* the poliomyelitis season.

2. Use all available vaccine immediately. Do not save it for "second shots," even though a sterilely punctured vial of vaccine can be kept under refrigeration without impairing either safety or potency of the vaccine.

3. The increasing supply of vaccine should be depended upon for second injections in 1956. The exact interval recommended between the first and second doses is not critical, so long as it is not *less* than two weeks. In fact, longer intervals seem to be advantageous. Therefore the second dose may be given at any time without losing the benefit of the first.

VACCINE SAFETY

On the question of the safety of the present Salk vaccine, little remains to be said. It is as safe as any biologic product can possibly be. It is doubtful whether any other therapeutic or prophylactic agent in common use is surrounded by as many safeguards as the present Salk vaccine. It may be said in passing that the very furore over the single accident that occurred in the spring of 1955 with the Salk vaccine has had the beneficial result of effecting more stringent safeguards on all biologic and bacteriologic products manufactured in the United States and has greatly encouraged the epidemiologic surveillance of all infectious diseases in the United States.

The Salk vaccine now used in the United States (and with slight modifications in other countries) is a "killed virus" trivalent, formalinized vaccine. Every lot released for use by the authority of the U.S. Public Health Service is assuredly safe, pure and potent.

The vaccine is manufactured in quantity by growing each of the three known types of poliovirus separately in tissue culture (minced monkey-kidney), filtering the virus fluid, treating it with formalin and heat, then mixing the three virus-vaccine pools to make one vaccine.

The detailed steps of manufacture, safety testing and potency testing are strictly governed by protocols of minimum standards enforced by the Public Health Service. As experience in manufacture and testing accumulates, these minimum standards are revised as needed. A manufacturing accident such as occurred in the spring of 1955 is now extremely unlikely, if not almost impossible.

A Technical Advisory Committee of the Public Health Service has taken full responsibility for maintaining vaccine safety. It has also investigated thoroughly the potential causes of risk with the vaccine. The members of this committee are Doctors David Bodian, Jonas E. Salk, Thomas Francis, Jr., Richard E. Shope, Carl Larson, Joseph E. Smadel, and James A. Shannon, Chairman.

Let me quote the summary of the Interim Report of this Committee issued on November 11, 1955, as follows:

> In summary, the Committee is of the opinion that the principal factors . . . involved in manufacturing difficulties have been identified and corrective measures have been taken.
>
> Among these factors is the absolute need for removal of particles within which virus may be protected from inactivation by formaldehyde. Provisions have been made to ensure as far as possible the removal of such protected particles by suitably spaced filtration procedures.
>
> In addition, the safety test program has been strengthened by improved sampling procedures in the tissue culture tests and by increasing the sensitivity of the monkey safety tests. These measures, together with continuous review of plant production records, assure the safety of released vaccine and should make possible an increased availability of vaccine.

A vast field trial of the Salk vaccine, the largest controlled experiment in medical history, was conducted in 217 field trial areas throughout the United States in 1954 under the sponsorship and at the expense of the National Foundation for Infantile Paralysis. Nearly 2 million children were kept under observation; 440,000 received three injections of vaccine; 210,000, injections of a placebo substance.

The results of the 1954 field trials were announced on April 12, 1955, by Dr. Thomas Francis at the University of Michigan, site of the independent Poliomyelitis Vaccine Evaluation Center. The "Francis report" concluded that the 1954 vaccine was safe; that it was 60 to 70 per cent effective in preventing paralytic poliomyelitis caused by type 1 poliovirus; and that it was 90 per cent or more effective against types 2 and 3.

Discussion of the safety of the present Salk vaccine is now an academic matter. It has become a question for historians rather than clinicians. Properly prepared Salk vaccine was administered to at least 15,000,000 children in the first year of its general availability. Reactions to it were exceedingly rare, slight and minimal. If the theoretical objections formerly urged against the Salk vaccine were of any practical significance, their effect would by this time be quite evident.

"PROVOKING" EFFECT

The question of the possible "provoking" effect of Salk vaccine injections continues to arise, although it would seem to be settled. A careful review of experience with the use of Salk vaccine in 1954 and 1955 indicates that it did not occur. The risk, if not theoretical, is at least minimal.

On the question of whether Salk poliomyelitis vaccine should be given during the poliomyelitis season, or under epidemic conditions, the answer is yes.

On this point a committee of physicians and poliomyelitis experts, representing the American Academy of General Practice, the American Academy of Pediatrics, the American Medical Association, the American Public Health Association, the Association of State and Territorial Health Officers, the U.S. Public Health Service and the Vaccine Advisory Committee of the National Foundation for Infantile Paralysis, came to the following unanimous conclusion on June 18, 1955:

> First of all, poliomyelitis vaccine has been shown to reduce greatly the incidence of paralytic poliomyelitis and particularly the incidence of severe and fatal cases. Secondly, the vaccine is expected to produce some antibody as early as a week to 10 days following the first shot, and even small amounts of antibody may be expected to have some effect in preventing paralytic poliomyelitis after this time. For this reason, the onset of an antibody response to the vaccine may eliminate any subsequent provoking effect of the vaccine injection.
>
> In summary, those at the meeting agreed that the total preventive effect of the vaccine in a period of rising poliomyelitis incidence should be much greater than the possible hazard from the provoking effect of the injection. Those present also concluded that the benefit to be gained by poliomyelitis immunization, in contrast to the small potential risk of provocation, increases in proportion to the severity of the poliomyelitis incidence, since a large number of paralytic poliomyelitis cases should be prevented during the entire period of the epidemic.
>
> Therefore the slight hazard of provocation is insufficient to limit the injection of poliomyelitis vaccine even in the presence of a rising incidence of poliomyelitis in the community.

The possibility that the Salk vaccine itself may exert a provoking effect, such as that reported with the injection of penicillin and pertussis vaccine, is further minimized by the fact that the vaccine is a "bland" solution. It is essentially a balanced salt solution with only a trace of protein.

Even the evidence that injected materials other than the Salk vaccine increase the risk of paralytic poliomyelitis during the poliomyelitis season is scanty. What can be said with assurance is only that if paralytic poliomyelitis does appear, it is more likely to be localized in the injected extremity. During field trials with gamma globulin in Iowa in 1952, children used as control subjects were injected with a gelatin substance. In spite of the severe epidemic conditions among the vulnerable age groups in this field trial area, there was little "provoking"

effect among the gelatin-injected children as compared to children in the same age group who received no injections at all.

USE OF SALK VACCINE IN EPIDEMIC SITUATIONS

On the basis of present evidence there is no contraindication to the widespread administration of Salk vaccine in a period of rising incidence of diagnosed and reported cases of poliomyelitis, paralytic and nonparalytic. The evidence accumulated in 1955 on the effectiveness of even one injection of the Salk vaccine would suggest that immediate vaccination of the entire unvaccinated population (at least up to the ages of 35 or 40) would offer the best hope of aborting the epidemic.

REVISED CONTRAINDICATIONS FOR ADMINISTERING SALK VACCINE

Contraindications for the administration of Salk vaccine have been slightly revised in the light of accumulating experience. "Mild" illness in nonpoliomyelitis seasons is no longer a contraindication. The following statements sum up current thinking on contraindications:

1. The vaccine should not be given during a major acute illness.

2. The vaccine should not be given during the summer ("polio season") or during epidemics of poliomyelitis to persons who are exhibiting symptoms of minor illness, especially fever, sore throat or gastrointestinal upset.

These contraindications apply to all immunizing biologicals.

3. The vaccine should not be given to persons in a household where a case of poliomyelitis has just occurred. The chances are that by the time the index case is diagnosed, almost all other members of the household will already and currently be infected with poliovirus.

The reasons for this contraindication are twofold: the injection of the vaccine will do absolutely no good *at this time*, and there is the minimal risk that the process of injection will do harm in persons in whom it may be almost positively presumed that virus is already multiplying (and probably being excreted).

It must be recognized that the ratio of poliovirus infection to clinically diagnosed and laboratory-confirmed poliomyelitis, paralytic or nonparalytic, is of the order of one to several hundred. Fox[4] has recently estimated it in a Louisiana study at one to 700.

The time of appearance of antibodies following a single injection of the Salk "killed-virus" vaccine is about seven to 10 days thereafter. In a person already infected with poliovirus the presence of comparatively large amounts of live virus will already be inducing antibody produc-

tion at a faster rate and earlier date than the injection of the small amount of killed virus in the Salk vaccine can possibly effect.

It is only under conditions of intimate personal contact, such as prevails in households and institutions, that the Salk vaccine is contraindicated after the discovery of an index case. In such cases it may be presumed that close to 100 per cent of the nonimmune population of the household or institution is already infected.

The situation in a community or neighborhood is quite different. Close to 100 per cent infection of the nonimmune population should *not* be presumed. Hence if an index case is discovered in a neighborhood, or a group of diagnosed cases suggest the threat of a poliomyelitis epidemic in a community, immediate vaccination of all but the already infected households (and intimate contacts of these households) is indicated. Under these circumstances the minimal risk of provoking (or localizing) paralysis in an already infected person is much less than the risk of contracting paralytic poliomyelitis.

The fundamental purpose of administering Salk vaccine, of course, is to prevent paralysis, not to prevent infection. The vaccine is of no use in the treatment of poliomyelitis, for the reasons already outlined.

EFFECTIVENESS OF THE SALK VACCINE

The Salk vaccine has turned out to be even more effective than was originally anticipated. A great deal of documentation on this point is now available. Its effectiveness, Salk's research has shown, is probably proportional to the amount or mass of antigen that actually gets into the body. It is this result which shows up in the statistical and epidemiologic reports. The following graphs, charts and figures are based on 1955 experience.

Figure 15 shows paralytic poliomyelitis attack rates among vaccinated and unvaccinated children based on preliminary reports from 11 states and New York City through November 1, 1955. This chart provided one of the first broad-scale indications of the effectiveness of the Salk vaccine. It indicated how effective even one dose of vaccine could be, since most children in 1955 got only one dose.

Figure 16 shows the drop in acute poliomyelitis hospital admissions among vaccinated age groups in the United States in 1955. In 1955 there was a sharp drop in the number of seven and eight year old children admitted to hospitals under a diagnosis of acute poliomyelitis. This is strong confirmatory evidence of the effectiveness of the Salk vaccine, for seven and eight year olds were those who received the great bulk of inoculation with the vaccine available in 1955.

The figures used in the age-distribution study summed up in Figure

16 were based on reports to the National Foundation for Infantile Paralysis of actual admissions of poliomyelitis patients to hospitals during a June-to-November period in 1955, compared with a similar period in 1954.

The hospital admission rates for poliomyelitis in 1955 dropped 52 per cent in the eight year old group and 40 per cent in the seven year

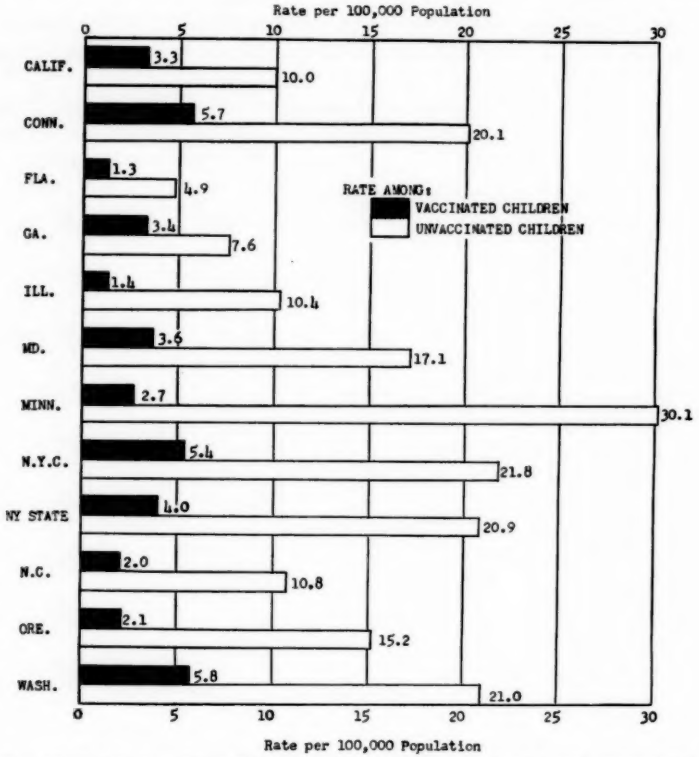


Fig. 15. Paralytic poliomyelitis attack rates among vaccinated and unvaccinated children, based on preliminary reports from 11 states and New York City through November 1, 1955. (Poliomyelitis Surveillance Unit, U.S. Public Health Service.)

old group. This contrasts with a decline of only seventeen per cent for the total population. Among young people aged 15 to 19 who did not receive the vaccine, the hospital admission rate decreased by only 12 per cent. While the total incidence of poliomyelitis in 1955 was somewhat (approximately 25 per cent) lower than in 1954, this would not account for the sharp change in age distribution of hospitalized cases.

Extremely important evidence of the effectiveness of the Salk vaccine comes from 1955 experience in the state of Massachusetts, where a severe epidemic occurred. Over 3900 cases of poliomyelitis were reported in this state alone. Nevertheless, so far as paralytic consequences were concerned, the Salk vaccine proved highly effective. This was al-

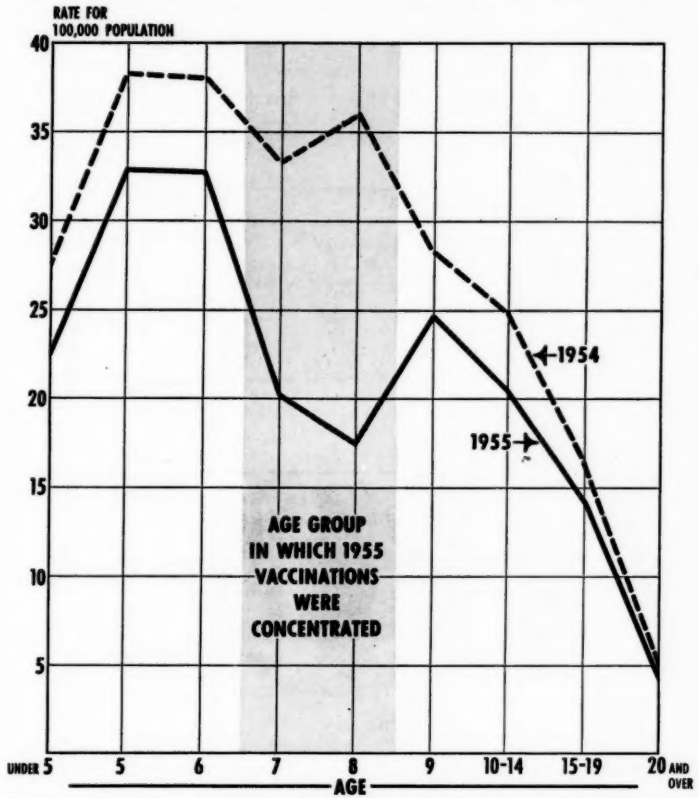


Fig. 16. Drop in acute poliomyelitis hospital admissions among vaccinated age groups. (Based on data for June 20–November 6, 1954, and June 26–November 19, 1955, compiled by the National Foundation for Infantile Paralysis.)

most exclusively a type 1 virus epidemic. In preventing paralytic cases, the vaccine effectiveness was 60 per cent, practically the same as that observed by Francis for protection against type 1 infections during the 1954 field trials.

Figure 17 shows the paralytic poliomyelitis attack rate by vaccination status in Massachusetts in 1955. Note that the paralytic attack rate among children who received no vaccine was 157 cases per 100,000

study population; it was over two and one-half times as high as the rate among children who received at least one dose of vaccine. The rate among the one-dose-vaccination children was 63 per 100,000, which is still a high rate. The attack rate fell with the increasing number of doses. However, the number of cases reported in the three- and four-dose calculations was not large enough to make them statistically significant. Nor should the false impression be gained that the effectiveness

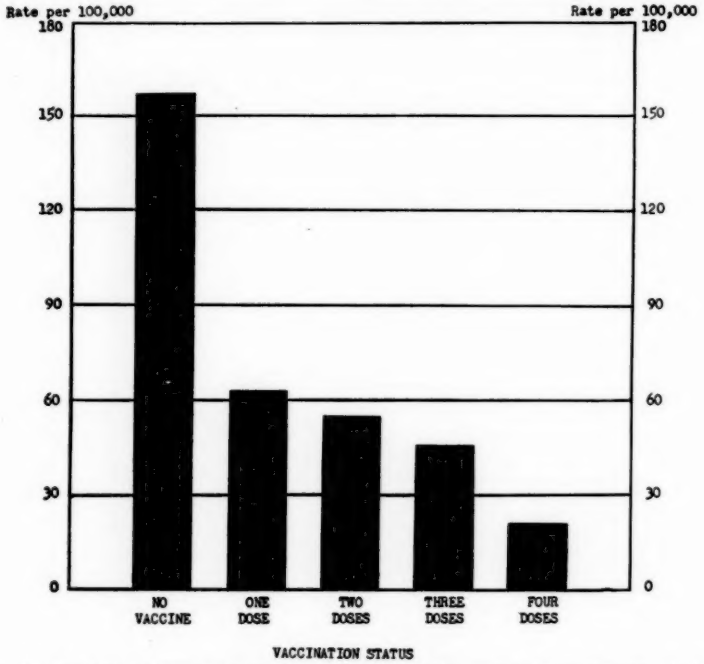


Fig. 17. Paralytic poliomyelitis attack rates by vaccination status, Massachusetts, 1955. (Massachusetts Department of Public Health.)

of the vaccine is in proportion to the number of doses except in terms of the ideal dosage schedules.

Table 20, from the New York State Department of Health, shows poliomyelitis rates by vaccination status in six to 10 year olds in New York State. It covers vaccination records for both 1954 and 1955. The table shows, in summary, that the paralytic attack rate among unvaccinated children was five times higher than in vaccinated children: 20.9 cases per 100,000 study population in the unvaccinated group, only 4.0 in the vaccinated group.

Attention is called particularly to a group of 23,370 children who

were vaccinated in 1954 as part of the vaccine field trial and received a "booster" dose of vaccine in 1955 as part of the 1955 vaccine program. No cases of paralytic poliomyelitis occurred in this group. These figures are not definitive, but they show a clear trend. Again, the children, 169,174 in number, who got two doses of vaccine in 1955 had a better record than those who got only one dose.

Canadian experience with Salk vaccine in 1955 also confirms its effectiveness (Table 21). Among 589,716 children who received two or more doses of vaccine in 1955 in Canada, there were just five observed

TABLE 20. *Poliomyelitis Rates by Vaccination Status in 6 to 10 Year Olds in Upstate New York*

(Preliminary Data, May 21 to October 21, 1955)

VACCINATION STATUS	POPULATION	CASES*				RATES PER 100,000		
		P	NP	U	T	P	NP	T
Vaccinated in 1954:								
Booster in 1955	23,370	0	8	0	8	—	34.2	34.2
No booster	74,330	4	18	1	23	5.4	24.2	30.9
Vaccinated in 1955:								
One dose	185,695	9	63	1	75	5.0	34.1	41.3
Two doses	169,174	5	39	3	47	3.0	23.1	27.8
Total vaccinated	448,569	18	128	5	153	4.0	28.5	34.1
Total unvaccinated	282,000	59	111	8	178	20.9	39.4	63.1

* Does not include 8 cases for which vaccination status is not known. *P*—paralytic; *NP*—nonparalytic; *U*—unspecified; *T*—total.

Data compiled by Dr. William Beadenkopf, Bureau of Epidemiology and Communicable Disease Control, and Dr. David Poskanzer, Epidemic Intelligence Service Officer assigned to New York State.

cases of paralytic poliomyelitis—a rate of 0.84 per 100,000 vaccinated population. Among 885,000 unvaccinated children there were 51 cases of paralytic poliomyelitis—a rate of 5.76 per 100,000 among the unvaccinated. These differential rates would indicate that the Salk vaccine as used in Canada in 1955 was about 85 per cent effective in preventing paralytic poliomyelitis. The slight advantage in the Canadian figures probably depends upon the conditions of use—generally, two doses instead of one—rather than upon any better quality of the Canadian vaccine.

A summary of U.S. vaccine experience in 30 states in 1955 is shown in Figure 18. There were 275 cases of paralytic poliomyelitis among 4,828,975 children who were vaccinated; 1398 cases among 5,237,768 unvaccinated children of the same ages. The case rate for the unvaccinated children was nearly five times as high as for the vaccinated children.

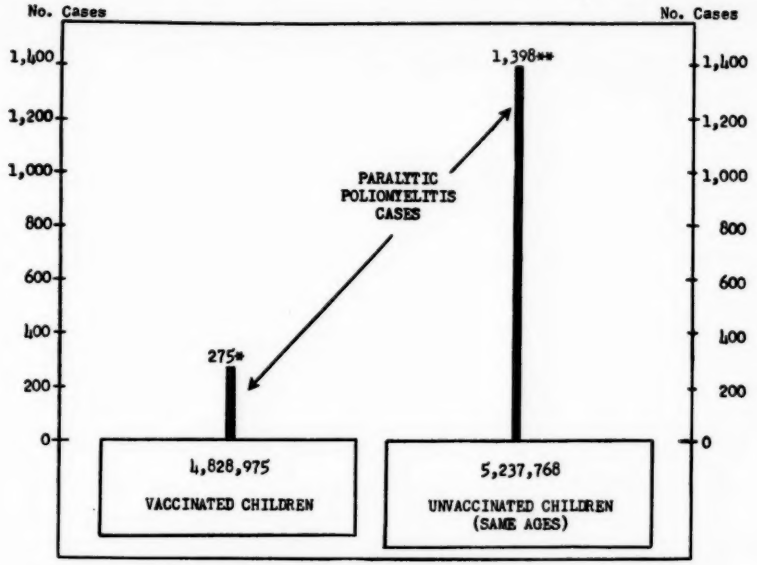
TABLE 21. *Number of Canadian Children of Specified Ages Receiving 2 or More Doses of Vaccine by July 1, 1955, and Number of Reported Paralytic Cases and Attack Rates in Vaccinated and Unvaccinated Populations, July 1–November 30, 1955*

PROVINCE	AGES* CONSIDERED	NO. VACCINATED 2 OR MORE DOSES	OBSERVED PARALYTIC CASES IN VACCINATED	RATE/100,000 POPULATION IN VACCINATED	NO.† NOT VACCINATED	OBSERVED PARALYTIC CASES IN NONVACCINATED	RATE/100,000 POPULATION IN NONVACCINATED
Newfoundland	5	3,412	0	0.00	8,700	0	0.00
Prince Edward Island	5–8	4,855	0	0.00	5,400	3	55.55
Nova Scotia	5–8	15,551	0	0.00	46,600	10	21.45
New Brunswick	5–10	24,000	0	0.00	58,400	1	1.71
Quebec	5–9	62,850	1	1.59	476,700	20	4.19
Ontario	5–10	306,311	2	0.65	200,000	4	1.99
Manitoba	5–9	51,333	0	0.00	31,900	0	0.00
Saskatchewan	5–6 Grades	27,528	0	0.00	11,700	0	0.00
Alberta	1–4	48,809	2	4.09	33,000	3	9.09
British Columbia	5–7	45,067	0	0.00	12,500	10	80.00
Canada		589,716	5	0.84	885,000	51	5.76

* For purposes of comparison, children of the ages specified only have been included. For example, a substantial number of children in the Province of Quebec under 5 years of age who received 2 doses of the vaccine have not been included.

† Since some figures are based on age group estimates, all have been rounded to the nearest hundred.

From the Department of National Health and Welfare, Ottawa, Canada.



* Case rate per 100,000 vaccinated children, 5.7
** Case rate per 100,000 unvaccinated children 26.7

Fig. 18. Number of paralytic poliomyelitis cases among children who received one or more inoculations of vaccine and among unvaccinated classmates, 30 states, 1955. (From state health department reports, compiled by the National Foundation for Infantile Paralysis.)

HOPES FOR 1956

Even with the highly effective Salk vaccine, and others that may in the future be developed, it is too early to speak of the "elimination" of paralytic poliomyelitis. And it is far too early to abandon the skills and facilities that have been developed for the treatment of poliomyelitis and the prevention of paralysis and deformity.

A tremendous challenge has been set before the American medical profession and its ancillaries by the development and testing of the Salk vaccine and the hope of using it so that paralytic poliomyelitis may eventually be eliminated. It seems worth while, therefore, to suggest what may be the immediate outcome of acceptance of the task of speedily inoculating millions of U. S. children between the ages of six months and 15 years—and pregnant women—with the Salk vaccine.

Figure 19 represents frankly a speculation on the possibility of the prevention of paralytic poliomyelitis in 1956.

We start with the total number—100 per cent—of *paralytic* cases of poliomyelitis that might occur at all ages in the United States in 1956.

This number is somewhat but not absolutely unpredictable. We have previous records to guide us. Most importantly we have experience with the ratio of total cases of poliomyelitis reported to paralytic cases diagnosed. This experience is based partly on U.S. Public Health Service records and partly on records kept by the National Foundation for Infantile Paralysis concerning a great number of hospitalized poliomyelitis cases. On this basis we can estimate that something over half, somewhere between 50 and 55 per cent, of diagnosed cases of poliomyelitis are paralytic. It is recognized that the borderline between paralytic and nonparalytic is not always sharply marked and that full-

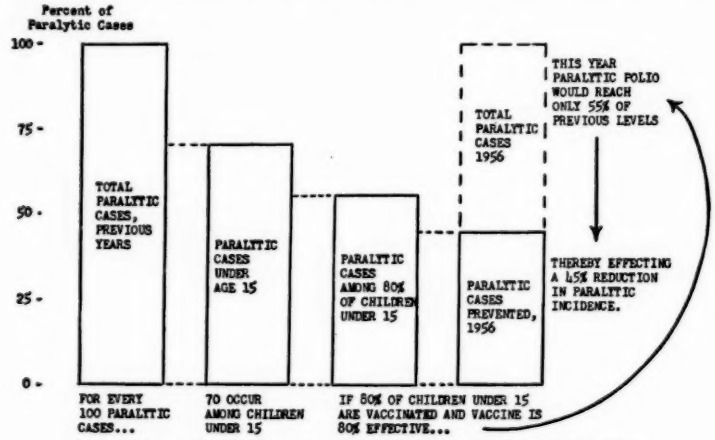

Percent of Paralytic Cases
100
75
50
25
0
TOTAL PARALYTIC CASES, PREVIOUS YEARS
PARALYTIC CASES UNDER AGE 15
PARALYTIC CASES AMONG 80% OF CHILDREN UNDER 15
TOTAL PARALYTIC CASES 1956
PARALYTIC CASES PREVENTED, 1956
THIS YEAR PARALYTIC POLIO WOULD REACH ONLY 55% OF PREVIOUS LEVELS
THEREBY EFFECTING A 45% REDUCTION IN PARALYTIC INCIDENCE.
FOR EVERY 100 PARALYTIC CASES...
70 OCCUR AMONG CHILDREN UNDER 15
IF 80% OF CHILDREN UNDER 15 ARE VACCINATED AND VACCINE IS 80% EFFECTIVE...

Fig. 19. Prevention of paralytic poliomyelitis—speculations for 1956.

scale muscle testing and examination must be done to reveal some of the minimal grades of residual paralysis or muscle weakness.

The second column presents the percentage of cases of paralytic poliomyelitis that occur in patients under 15 years of age. There is a wealth of statistical material on age-specific case rates for paralytic poliomyelitis. One interesting fact is not shown in this chart: namely, the number of cases in the higher age ranges has been constantly increasing in the United States, so that around 25 per cent of the diagnosed cases now occur in adults. They are often more serious than in children. Pregnant women, for example, appear to be about 1.6 to 2.0 times as susceptible to paralytic poliomyelitis as nonpregnant women in the same age groups.

The second column in Figure 19 shows, on the basis of previous records, that for every 100 cases of paralytic poliomyelitis diagnosed, about 70 will occur in children under 15 years of age.

The third column is just four fifths as high as the second column; and the fourth column, within the black lines, is also four fifths of the third column.

The third column makes the supposition that 80 per cent of the children under 15 in the United States will be vaccinated against paralytic poliomyelitis before the 1956 season. This is the big "if," which depends primarily, I believe, on available vaccine supply.

The 80 per cent factor in the fourth column is not, however, an "if." It is the fact already documented that the Salk vaccine is about 80 per cent effective in the prevention of paralytic poliomyelitis. This figure, based on 1955 experience, is, I believe, conservative. Later experience will push it up much higher.

The dotted line at the top of the fourth column simply indicates that if there were no Salk vaccine, and if there were no other effective means of preventing paralytic consequences of poliomyelitis infection, the total number of paralytic cases of poliomyelitis to be expected in 1956 in children under 15 years of age would be 100 per cent of whatever the epidemic circumstances of the year brought about. In other words, we could do nothing about it.

I direct your particular attention to the heavy black line about the middle of the fourth column. If you compare it with the percentage scale at the side of the first column, you will see that it comes up to the 45 per cent mark. The meaning of this figure can be put two ways.

It means that if our nationwide vaccine program for 1956 can be effectively implemented—in addition to what was already accomplished in 1955,—we have every reason to hope that the incidence of paralytic poliomyelitis will reach only about 55 per cent of otherwise anticipated levels. The other way of saying this is that if we concentrate our vaccine program for 1956 in the most susceptible age groups (which includes pregnant women, although they are not shown on this chart), we can expect to reduce the incidence of paralytic poliomyelitis by about 45 per cent. This would be a most dramatic reduction in a single year in the incidence of any disease.

Statistical calculations similar to those just outlined reveal that the reduction in the incidence of paralytic poliomyelitis in 1955 was something under 10 per cent. This figure has to take into consideration the conditions of use of the vaccine in 1955, when most children received only one injection. We estimate that in 1955 somewhere between 1200 and 1300 cases of paralytic poliomyelitis were prevented.

It is impossible at this time to put any accurate numbers for 1956 on the percentage figures illuminated in the chart in Figure 19. Paralytic poliomyelitis is still an unpredictable disease, and no one yet really knows how or why epidemics start or stop.

For public health and other administrative purposes on which decisions must be based, it is common to use five-year averages of the incidence of cases. In the five years 1950 through 1954, with an unvaccinated population in the United States, the average number of cases of poliomyelitis reported was around 40,000.

TABLE 22. *Number of Poliomyelitis Cases and Deaths Reported, Case and Death Rate per 100,000 Population*[a] *and Ratio of Death Rate to Case Rate, United States, 1936–1955*

YEAR	CASES REPORTED		DEATHS REPORTED		RATIO OF DEATH RATE TO CASE RATE (PER CENT)
	Number	Rate Per 100,000 Population	Number	Rate Per 100,000 Population	
1936	4,523	3.5	780	.6	17.1
1937	9,514	7.4	1,461	1.1	14.9
1938	1,705	1.3	487	.4	30.8
1939	7,343	5.6	773	.6	10.7
1940	9,804	7.4	1,026	.8	10.5
1941	9,086	6.8	807	.6	8.9
1942	4,167	3.1	561	.4	13.5
1943	12,450	9.3	1,151	.9	9.2
1944	19,029	14.3	1,361	1.0	7.2
1945	13,624	10.3	1,186	.9	8.7
1946	25,698	18.4	1,845	1.3	7.2
1947	10,827	7.6	580	.4	5.4
1948	27,726	19.0	1,895	1.3	6.8
1949	42,033	28.3	2,720	1.8	6.5
1950	33,300	22.0	1,904	1.3	5.7
1951	28,386	18.5	1,551	1.0	5.5
1952	57,879	37.2	3,145	2.0	5.4
1953	35,592	22.5	1,450	0.9	4.0
1954	38,476	23.9	1,620	1.0[b]	4.2[b]
1955	29,270[c]	17.8[c]	N.A.	N.A.	N.A.

Note: Morbidity data for earlier years should be interpreted with caution because of probable under-reporting of less serious cases.

[a] Based on midyear population estimates of states reporting, Bureau of the Census.

[b] Based on 10% sample of death certificates.

[c] Provisional data.

N.A.—Data not available.

(From the United States Public Health Service.)

Solely by way of illustration—and not in any sense a prediction—it could be calculated under the conditions of Figure 19, and on the unpredictable assumption that the number of cases of paralytic poliomyelitis which might have occurred in the United States in 1956 would be close to the five-year average number of cases, that the number of paralytic poliomyelitis cases in 1956 would be on the order of 10,000 to 12,000. An examination of Table 22 will show why this must be an illustration only and not a prediction.

EPIDEMIOLOGIC AND STATISTICAL BASE LINES

Radical changes in the epidemiologic and statistical picture of paralytic poliomyelitis in the United States are bound to occur with the increasingly widespread use of the Salk vaccine.

As base lines against which these changes may be charted in the future, it will be valuable to have not only the nationwide data on total

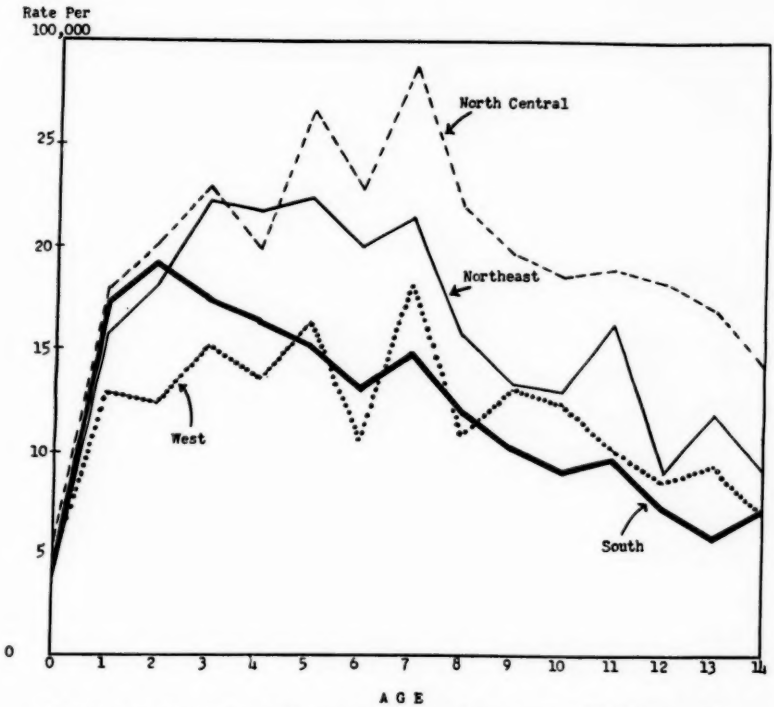


Fig. 20. Paralytic poliomyelitis age-specific admission rates per 100,000 population, by census region, 1953, as reported by hospitals to the National Foundation for Infantile Paralysis.

cases reported, death rates and the like, as shown in Table 22, but also more refined data on such matters as regional and seasonal attack rates. These are given here as a matter of record.

Significant geographic differences in the age selection of paralytic poliomyelitis are evident in tabulations of patient care notices received from hospitals by the National Foundation. These data include 10,071 paralytic cases with onset in 1953 and 11,965 paralytic cases with onset in 1954. Official U.S. Public Health Service figures for 1953 and 1954,

TABLE 23. *Paralytic Poliomyelitis Age—Specific Admission Rates per 100,000 Population, by Census Region, 1953, as Reported by Hospitals to NFIP*

AGE AT ONSET	U. S.		NORTHEAST		NORTH CENTRAL		SOUTH		WEST	
	Number Paralytic Cases	Rate Per 100,000	Number Paralytic Cases	Rate Per 100,000	Number Paralytic Cases	Rate Per 100,000	Number Paralytic Cases	Rate Per 100,000	Number Paralytic Cases	Rate Per 100,000
Total, all ages	10,071	6.4	2382	5.8	3866	8.3	2645	5.4	1178	5.4
Under 5	2,783	15.2	667	16.2	897	17.1	935	14.7	284	11.3
Under 1	165	4.3	31	3.6	61	5.5	53	3.9	20	3.7
1	613	16.5	130	15.7	193	17.9	224	17.2	66	12.8
2	666	18.3	149	18.2	211	20.1	244	19.1	62	12.3
3	694	19.8	179	22.1	231	22.9	212	17.4	72	15.1
4	645	18.3	178	21.7	201	19.9	202	16.4	64	13.5
5–9	2,733	17.6	667	18.8	1052	24.0	728	13.2	286	13.7
5	709	20.1	175	22.3	259	26.6	196	15.2	79	16.3
6	646	17.0	172	20.0	242	22.8	177	13.0	55	10.6
7	570	20.7	134	21.4	224	28.8	145	14.8	67	18.1
8	425	15.6	103	15.7	172	21.9	111	11.9	39	10.9
9	383	14.0	83	13.3	155	19.6	99	10.1	46	13.0
10–14	1,458	11.7	331	11.9	622	17.4	353	7.8	152	9.6
10	378	13.0	83	12.9	155	18.5	94	8.9	46	12.3
11	351	13.8	91	16.2	137	18.9	90	9.6	33	10.1
12	262	11.0	48	9.0	127	18.2	61	7.2	26	8.5
13	247	10.8	61	11.9	110	16.9	49	5.8	27	9.4
14	220	9.6	48	9.2	93	14.2	59	7.1	20	7.0
15 and over	2,878	2.6	673	2.2	1219	3.7	548	1.7	438	2.8
Age unspecified	219	—	44	—	76	—	81	—	18	—

TABLE 24. *Paralytic Poliomyelitis Age—Specific Admission Rates per 100,000 Population, by Census Region, 1954, as Reported by Hospitals to NFIP*

AGE AT ONSET	U. S.		NORTHEAST		NORTH CENTRAL		SOUTH		WEST	
	Number Paralytic Cases	Rate Per 100,000	Number Paralytic Cases	Rate Per 100,000	Number Paralytic Cases	Rate Per 100,000	Number Paralytic Cases	Rate Per 100,000	Number Paralytic Cases	Rate Per 100,000
Total, all ages	11,965	7.4	2203	5.3	2584	5.5	5606	11.3	1572	7.0
Under 5	3,280	17.6	511	11.9	697	13.2	1790	28.0	282	10.6
Under 1	205	5.2	27	3.0	42	3.7	122	9.2	14	2.5
1	747	19.5	93	10.4	147	13.3	448	34.7	59	10.9
2	822	22.1	129	14.7	168	15.8	463	36.8	62	11.9
3	750	20.6	127	15.5	167	16.5	377	29.2	79	15.0
4	756	21.5	135	16.7	173	17.6	380	31.2	68	13.5
5–9	2,998	18.3	638	16.9	652	13.9	1350	23.9	358	16.1
5	756	21.4	168	20.6	153	15.2	360	29.6	75	15.1
6	661	18.7	150	17.5	140	13.7	297	25.5	74	15.3
7	646	17.0	126	14.3	161	14.7	286	21.7	73	14.3
8	523	19.0	117	18.9	110	13.8	214	22.1	82	22.0
9	412	15.1	77	12.6	88	11.3	193	19.8	54	14.8
10–14	1,689	13.1	322	11.0	382	10.3	775	16.9	210	12.6
10	375	13.7	73	11.7	75	9.3	173	18.2	54	14.7
11	383	13.2	79	11.9	81	9.7	176	17.0	47	12.4
12	353	13.8	62	10.5	92	12.6	163	18.1	36	10.9
13	307	12.8	49	9.0	79	11.4	135	15.9	44	14.4
14	271	11.8	59	11.5	55	8.4	128	15.2	29	10.1
15 and over	3,814	3.4	705	2.3	822	2.4	1596	4.8	691	4.4
Age unspecified	184	—	27	—	31	—	95	—	31	—

respectively, include 10,798 and 14,404 cases identified as paralytic. Approximately 1000 hospitals reported admissions in these two years.

As shown in Table 23 and Figure 20, paralytic case rates in 1953 were highest in the South at ages one to three; in the Northeast, at ages three to seven; and in the North Central states, at ages five to

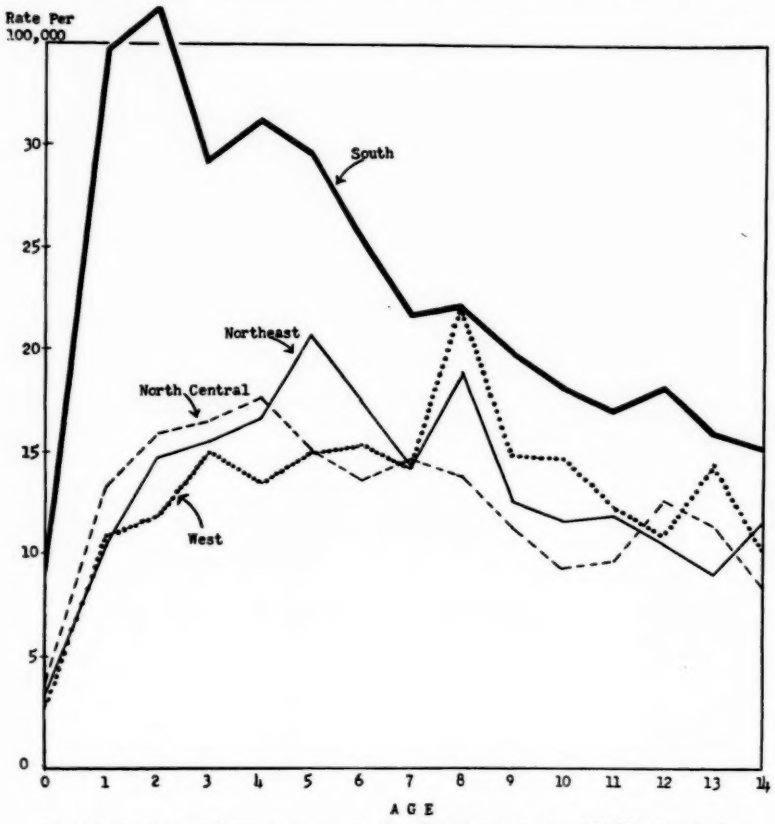


Fig. 21. Paralytic poliomyelitis age-specific admission rates per 100,000 population, by census region, 1954, as reported by hospitals to the National Foundation for Infantile Paralysis.

eight. In the West the age-specific attack rates form a broad irregular plateau from age one to age 10.

Although the focus of poliomyelitis incidence shifted from the northern states in 1953 to the southern states in 1954, similar age patterns are apparent in both years (see Table 24 and Fig. 21). Paralytic attack rates in the South in 1954 reached an abrupt peak at ages one

and two and thereafter declined continuously except for minor upward fluctuations at ages four, eight and 12. Maximum specific case rates in the other three regions occurred at older ages: age four in the North Central area, age five in the Northeast and age eight in the West.

These regional variations may be pertinent to the future demonstration of the effectiveness of vaccination programs.

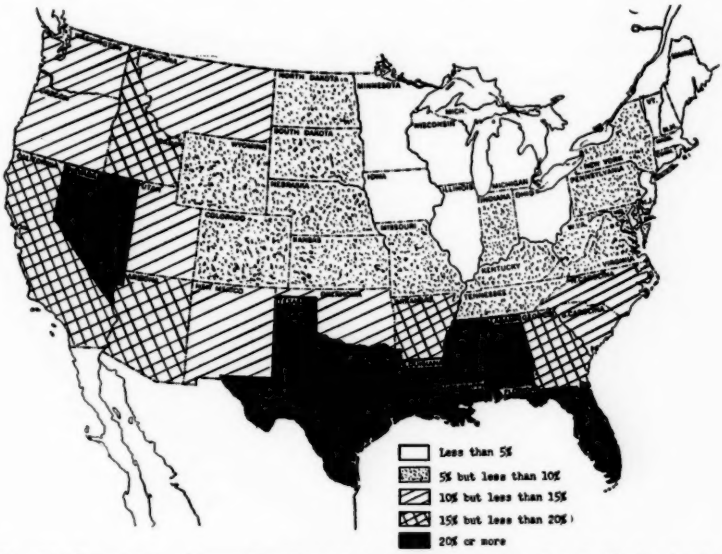


Fig. 22. Percentage of annual poliomyelitis cases reported in first half of calendar year, by state, 1951–55 average. (From U.S. Public Health Service.)

Figure 22 shows in detail by states the well known seasonal incidence of poliomyelitis. In general, poliomyelitis moves from south to north with the advent of warmer weather. There is some variation from this pattern on the Pacific coast and in the Mountain states. It is interesting to observe that the regional lines that might be drawn on this map would parallel those found on "garden maps" of planting seasons in different parts of the United States.

SUMMARY AND CONCLUSIONS

The ideal dosage schedule for the Salk poliomyelitis vaccine, as presently constituted, is two 1-cc. doses, intramuscularly, spaced two to six weeks apart, with a booster dose of 1 cc. given at least seven months to one year later. The schedule of injections should ideally start during the second six months of life.

Because of possibly limited vaccine supplies, a compromise or emergency dosage schedule may have to be used in 1956. All available vaccine supplies should be used immediately. Booster doses should be postponed until vaccine supplies are fully utilized for primary immunization.

Properly processed and tested Salk vaccine is safe—as safe as any biological product can possibly be. The question of vaccine safety is now largely historical.

Contraindications for administration of the Salk poliomyelitis vaccine have been slightly revised. The vaccine should not be given (1) during major acute illness; (2) during the poliomyelitis season to persons exhibiting symptoms of minor illness, especially fever, sore throat and gastrointestinal upset; and (3) to those in intimate household or institutional contact with an index case of poliomyelitis.

The risk of provoking paralysis by a first injection of Salk vaccine is minimal. If primary sensitization has occurred, the risk in subsequent vaccine injections is probably nil.

The best hope of aborting an epidemic of poliomyelitis is to give one injection of the Salk vaccine immediately to the entire unvaccinated population in the community up to age 35 or 40. Households with index cases should be excepted.

The demonstrated effectiveness of the Salk vaccine, under conditions of use in 1955, was approximately 80 per cent. It was somewhat less effective against type 1 poliovirus infections and epidemics.

Detailed records of the past incidence of poliomyelitis, paralytic and nonparalytic, with an entirely unvaccinated population in the United States, are provided. These may serve as a base line for determining the long-range effects of programs of vaccination against paralytic poliomyelitis.

The statistical and epidemiologic picture of poliomyelitis in the United States is rapidly changing as the result of the increasingly widespread use of all available supplies of the Salk vaccine. The World Health Organization has recommended that all countries "with a high incidence of paralytic poliomyelitis should plan to bring vaccination into routine use at an early date."

If efforts are successful to vaccinate a high proportion of the most susceptible age groups in the American population—children aged six months through 14 years and pregnant women—before the advent of the 1956 poliomyelitis season, a reduction by 45 per cent in the number of paralytic cases that might otherwise have occurred in 1956 is well within reason. This would represent a most dramatic reduction in a single year. The cooperation of the medical profession is essential to this possible result.

REFERENCES

1. Brown, G. C.: Effect of Booster Inoculations on the Serologic Status of Children Vaccinated with Poliomyelitis Vaccine. *Am. J. Pub. Health*, 45:1401, 1955.
2. Brown, G. C., and Smith, D. C.: Immunization of Infants and Pre-school Children with Poliomyelitis Vaccine. *Federation Proc.*, 14:458, 1955.
3. Committee on Typing of the National Foundation for Infantile Paralysis: Immunologic Classification of Poliomyelitis Viruses. VII. Discussion of Results and General Summary of the Co-operative Program for the Typing of 230 Strains. *Am. J. Hyg.*, 58:74, 1953.
4. Fox, J. P., and others: A Continuing Study of the Acquisition of Natural Immunity to Poliomyelitis in Representative Louisiana Households. Presented at the 83rd annual meeting of the American Public Health Association, Kansas City, Mo., November 15, 1955.
5. Francis, T., and others: An Evaluation of the 1954 Poliomyelitis Vaccine Field Trials: Summary Report. *Am. J. Pub. Health*, 45:Part II, 1955.
6. Langmuir, A. D., and others: Surveillance of Poliomyelitis in the United States in 1955. *Am. J. Pub. Health*, to be published.
7. Pope, A. S., and others: Evaluation of Poliomyelitis Vaccination in Massachusetts. *New England J. Med.*, 254:3, 1956.
8. Public Health Service: Interim Report of Technical Committee on Poliomyelitis Vaccine, Nov. 11, 1955. *J.A.M.A.*, 159:1444, 1955.
9. Public Health Service: Progress Report on the Poliomyelitis Vaccination Program, January 24, 1956.
10. Salk, J. E.: Poliomyelitis Vaccine in the Fall of 1955. *Am. J. Pub. Health*, 46:1, 1956.
11. Salk, J. E., Scheele, L. A., Dublin, T. D., and Francis, T.: Symposium on Poliomyelitis. *J.A.M.A.*, 158:14, 1955.
12. Van Riper, H., ed.: Information for Physicians on the Salk Poliomyelitis Vaccine. New York, National Foundation for Infantile Paralysis, 1955.
13. Van Riper, H., ed.: New Information for Physicians on the Salk Poliomyelitis Vaccine, #2. New York, National Foundation for Infantile Paralysis, 1956.
14. World Health Organization: Poliomyelitis Vaccination: A Review of the Present Position at a Meeting of Experts Convened by the World Health Organization in Stockholm, Sweden, Nov. 21, 1955. Mimeographed report issued by WHO, Nov. 29, 1955.

120 Broadway
New York 5, New York

CUMULATIVE INDEX

(February—May)

Page numbers of symposium and clinic titles are given in **boldface** type.

ABDOMEN, distress, as symptom of polyp, *Feb.*, 97
roentgen examination, in obstruction of colon, *Feb.*, 81
Abscess. See also under names of organs and regions.
pericolonic, as indication for operation in ulcerative colitis, *Feb.*, 161
Achromycin. See *Tetracycline(s)*.
Acid, hydrochloric, in rectal procidentia, *Feb.*, 119
mandelic, in urogenital tract infections, *May*, 372
para-aminosalicylic, absorption, *May*, 247
administration, *May*, 248
chemistry, *May*, 246
dosage, *May*, 248
excretion, *May*, 247
historical account, *May*, 246
in tuberculosis, *May*, 365, 428, 429, 434
pharmacodynamic action, *May*, 246
toxicity, *May*, 248
tannic, in barium study of colon, *Feb.*, 30, 31
Acidosis, *Feb.*, 57
Actinomycosis, *May*, 416
Adenitis. See *Lymphadenitis*.
Adenoidal-pharyngeal-conjunctival viruses, infections due to, diagnosis, *May*, 355
Adenomas, anorectal, biopsy, *Feb.*, 23
Adenomatosis. See *Colon, polyposis*.
Adrenocortical preparations, cortisone, in tuberculous meningitis, *May*, 435
hydrocortisone, in Waterhouse-Friderichsen syndrome, *May*, 392, 393
in fulminating meningococcemia, *May*, 275
Aerosporin. See *Polymyxin*.
Age, at time of infection, as prognostic factor in tuberculosis, *May*, 427
factors, in respiratory tract diseases, *May*, 359
Age of infection when first diagnosed, as prognostic factor in tuberculosis, *May*, 428
Albamycin. See *Streptonivicin*.
Alficetyn. See *Chloramphenicol*.
Alkalosis, *Feb.*, 57
Allergic reactions to antibiotics, *May*, 439
Amebiasis, *Feb.*, 170–76; *May*, 414
extraintestinal, *Feb.*, 175
Amebiasis cutis, *Feb.*, 176
Ameboma, *Feb.*, 175
Analeptics in ulcerative colitis, *Feb.*, 157
Analgesia, regional, in proctologic surgery, *Feb.*, 63
Anaphylactic reactions to antibiotics, *May*, 440
Anatomy, variational, of colon, *Feb.*, 3
Anesthesia, for endoscopy, *Feb.*, 20
for proctology, *Feb.*, **53–66**
agents, *Feb.*, 60
anatomic considerations, *Feb.*, 53
fundamentals, *Feb.*, 53
induction, *Feb.*, 59
physiologic considerations, *Feb.*, 53
postoperative management, *Feb.*, 64
preanesthetic medication, *Feb.*, 58
preoperative preparation, *Feb.*, 56
provision for minimal resistance to breathing, *Feb.*, 56
techniques, *Feb.*, 60
Anorectum. See also *Anus* and *Rectum*.
bleeding from, *Feb.*, 16
disease, *Feb.*, **113–25**
excretions, *Feb.*, 16
pain in, *Feb.*, 16
protrusion through, *Feb.*, 15
Anoscope, *Feb.*, 19
Antepar. See *Piperazine hexahydrate*.
Antibiotics. See also under names of particular drugs, as *Penicillin; Streptomycin;* etc.
absorption, gastrointestinal, after oral administration, *May*, 449
administration, routes of, *May*, 450

Antibiotics, and chemotherapeutic agents, therapeutic dosages and routes of administration, *May*, 452, 453, 454
bacterial resistance to, *May*, 346
bacterial susceptibility to, *May*, 448
broad-spectrum, antagonism to penicillin, *May*, 269
choice of, *May*, 448
combinations, *May*, 450
administration, routes of, *May*, 455
commercially available, *May*, 455
dosages, *May*, 448
and routes of administration, *May*, **447–56**
failure, *May*, 451
in cellulitis, *May*, 272
in diarrhea, *Feb.*, 149
in diphtheria contacts, prophylactic, *May*, 275
in furunculosis, *May*, 272
in localized infections, *May*, 229
in mastoiditis, *May*, 273
in meningitis, *May*, 274
in otitis media, *May*, 273
in resistant infections, *May*, 349
in soft tissue abscess, *May*, 272
in ulcerative colitis, *Feb.*, 158
in Waterhouse-Friderichsen syndrome, *May*, 275
infections resistant to, management, *May*, 348
mechanism of action, current knowledge of, *May*, **223–34**
neurotoxicity, *May*, 441
prophylactic use, *May*, 451
reactions, accidental, *May*, 442
allergic, *May*, 439
anaphylactic, *May*, 440
miscellaneous, *May*, 443
systemic, *May*, 440
research, *May*, 451
systemic, *May*, 224
therapy, relation to hormonal therapy, *May*, 231
toxicology, *May*, **439–45**
vitamin deficiency due to, *May*, 443
Antimicrobial agents. See also *Antibiotics*.
combinations, *May*, **345–52**
clinically useful, in resistant infections, *May*, 349
synthetic, applied pharmacology, *May*, **235–57**
Antimicrobial therapy, and diagnosis, in infections of respiratory tract, *May*, **353–67**
in cardiovascular infections, *May*, **399–406**
Antimicrobial therapy, in gastrointestinal tract infections, *May*, **407–26**
in genitourinary tract infections, *May*, **369–76**
symposium on, *May*, **221–456**
Antispasmodics in ulcerative colitis, *Feb.*, 157
Anus. See also *Anorectum* and *Rectum*.
abnormalities, types, *Feb.*, 67
abscess, *Feb.*, 122–24
atresia, roentgen examination, *Feb.*, 29
fissure, *Feb.*, 119–22
fistula, *Feb.*, 122
imperforate, *Feb.*, 67
and associated anomalies, *Feb.*, **67–77**
stenosis, congenital, *Feb.*, 67
APC viruses. See *Adenoidal-pharyngeal-conjunctival viruses*.
ARD. See *Respiratory tract, disease, acute, undifferentiated*.
Aureomycin. See *Chlortetracycline*.
Autonomic nervous system. See under *Nervous system*.

Bacitracin, *May*, 340
absorption, *May*, 341
administration, *May*, 342
routes of, *May*, 453, 454, 455
antimicrobial activity, *May*, 340
clinical use, *May*, 342
distribution, *May*, 341
dosage, *May*, 342, 453, 454
excretion, *May*, 341
in amebiasis, *May*, 415
in infections, *May*, 343
in pulmonary infections, *May*, 364
in shigellosis, *May*, 336
polymyxin and neomycin, applied pharmacology, *May*, **329–44**
preoperative use, *May*, 339, 343
toxicity, *May*, 341
Bacteria, culture, in proctologic examination, *Feb.*, 25
dependence on streptomycin, *May*, 289
diarrhea due to, *Feb.*, 143
nonsusceptible, overgrowth due to antibiotics, *May*, 442
resistance, to antibiotics, *May*, 346
to erythromycin, *May*, 313
to penicillin, *May*, 269
to streptomycin, *May*, 288
sensitivity to drugs used in meningitis, *May*, 386
susceptibility to antibiotics, *May*, 448
Balantidiasis, *Feb.*, 176–7
Barbiturates in proctologic anesthesia, *Feb.*, 61

Barium study of colon. See under *Colon.*
Barium sulfate in colon studies, *Feb.*, 30
BCG. See under *Tuberculosis, vaccine.*
Bicillin. See *Benzathine penicillin G* under *Penicillin, preparations.*
Biopsy, proctologic, *Feb.*, 23
Bismuth glycolylarsanilate in amebiasis, *Feb.*, 174
Bleeding. See *Hemorrhage.*
Blood, dyscrasias, due to antibiotics, *May*, 441
  reactions, to chloramphenicol, *May*, 322
  sedimentation rate, in proctologic examination, *Feb.*, 26
  swallowed, rectal bleeding due to, *Feb.*, 209
  tests, chemical, in proctologic examination, *Feb.*, 25
  transfusion, in diarrhea, *Feb.*, 147
  venous return from rectum, *Feb.*, 8
Bones, tuberculosis of, *May*, 436
Bowel. See *Intestine(s).*

C VIRUS. See *Coxsackie virus.*
Candidiasis, *May*, 417
Carbomycin, *May*, 313
  administration, routes of, *May*, 453, 455
  dosage, *May*, 453
Carbon dioxide, elimination, during anesthesia, *Feb.*, 56
Cardiovascular infections, antimicrobial therapy, *May*, **399–406**
Cathocin. See *Cathomycin.*
Cathomycin, *May*, 313
  in pulmonary infections, *May*, 364
Cecum, *Feb.*, 3
  lymphatic drainage, *Feb.*, 7
Cerebral edema, recognition and management, *May*, 393
Cerebrospinal fluid, changes, in central nervous system disease, *May*, 380
Chemotherapy in ulcerative colitis, *Feb.*, 158
Chloramphenicol, absorption, *May*, 318
  administration, intramuscular, *May*, 320
    intravenous, *May*, 321
    oral, *May*, 319
    rectal, *May*, 320
    routes of, *May*, 319, 453, 455
    topical, *May*, 321
  antimicrobial activity, *May*, 324
  applied pharmacology, *May*, **317–27**
  blood dyscrasias due to, *May*, 441
  chemical properties, *May*, 317
Chloramphenicol, distribution, *May*, 318
  dosage, *May*, 319, 453
  excretion, *May*, 318
  in gastrointestinal tract infections, *May*, 413
  in meningitis, *May*, 386
  in ornithosis, *May*, 361, 362
  in pulmonary infections, *May*, 364
  in rickettsial diseases, *May*, 361
  in urogenital tract infections, *May*, 373
  indications, *May*, 324
  mechanism of action, *May*, 227
  physical properties, *May*, 317
  reactions, untoward, *May*, 322
Chloromycetin. See *Chloramphenicol.*
Chloroquine in amebiasis, *Feb.*, 174
Chlortetracycline, absorption, *May*, 297, 298, 299
  administration, *May*, 299
    routes of, *May*, 452, 455
  chemical differentiation, *May*, 297
  dosage, *May*, 299, 452
  excretion, *May*, 299
  in cystic fibrosis of pancreas, *May*, 302
  in urogenital tract infections, *May*, 373
  mechanism of action, *May*, 228
  stability, *May*, 296
  toxicity, *May*, 300
Choriomeningitis, lymphocytic, diagnosis, *May*, 357
Cobalt, enhancement of penicillin efficiency, *May*, 226
Coccidioidomycosis, diagnosis, *May*, 358
  treatment, *May*, 365
Cold, common, diagnosis, *May*, 355
Colic, infantile, psychosomatic aspects, *Feb.*, 198
Colitis, rectal bleeding due to, *Feb.*, 212
  ulcerative, *Feb.*, **153–67**
    chronic, *May*, 421
      roentgen study, *Feb.*, 47
    psychosomatic aspects, *Feb.*, 204
Colon, abnormalities, congenital, roentgen study, *Feb.*, 33–9
    obstructive, *Feb.*, **79–91**
  anatomy, variational, *Feb.*, 3
  and rectum, anatomy, applied, *Feb.*, **3–13**
    neoplasms, *Feb.*, **93–111**
  atresia and stenosis, *Feb.*, 79–82
    roentgen study, *Feb.*, 38
  barium study, *Feb.*, 29
    barium mixtures, *Feb.*, 30
    preparation, *Feb.*, 30
    technique of examination, *Feb.*, 31

Colon, dilatation, megacolon, *Feb.*, 39–43
barium study, *Feb.*, 31
congenital, *Feb.*, 39, 40, 87–90, 134–6
roentgen findings, *Feb.*, 41
psychogenic, vs. congenital megacolon, *Feb.*, 132
roentgen examination, *Feb.*, 28
types, *Feb.*, 39
duplication, roentgen findings, *Feb.*, 38
lymphatic drainage, *Feb.*, 7
malignancy, as indication for operation in ulcerative colitis, *Feb.*, 161
nervous system, autonomic, *Feb.*, 9
normal, roentgen study, *Feb.*, 32
obstruction, roentgen examination, *Feb.*, 29
perforation, roentgen examination, *Feb.*, 29
polyposis, *Feb.*, 101–5
as indication for operation in ulcerative colitis, *Feb.*, 161
polyps, *Feb.*, 94
relation of mesenteric cysts and retroperitoneal hernia to, *Feb.*, 5
roentgenology, *Feb.*, **27–52**
plain film examination, *Feb.*, 27
rotation, errors of, *Feb.*, 33
roentgen findings, *Feb.*, 35
first stage, *Feb.*, 83
malrotation and, *Feb.*, 82–5
mechanism of, *Feb.*, 82
reversed, *Feb.*, 84
second stage, *Feb.*, 83
pathologic conditions, *Feb.*, 83
third stage, *Feb.*, 84
pathologic conditions, *Feb.*, 85
stenosis, *Feb.*, 79–82
stricture, as indication for operation in ulcerative colitis, *Feb.*, 161
tumors, polypoid, roentgen study, *Feb.*, 43
roentgen study, *Feb.*, 46
Compenamine. See *Penicilline G* under *Penicillin, preparations.*
Constipation, *Feb.*, **127–36**
psychogenic, *Feb.*, 128
psychosomatic aspects, *Feb.*, 199
spastic, *Feb.*, 132, 201
Cortisone. See under *Adrenocortical preparations.*
Coxsackie virus infection, diagnosis, *May*, 356
Croup, diagnosis, *May*, 360
Cryptitis, *Feb.*, 119
Cyclopropane in proctologic anesthesia, *Feb.*, 59, 61
Cyst, enteric. See *Intestine(s), duplications.*
enterogenous. See *Intestine(s), duplications.*
inclusion. See *Intestine(s), duplications.*
mesenteric, relation to colon, *Feb.*, 5
mesocolic, *Feb.*, 5
retroperitoneal, *Feb.*, 5
thoracic. See *Intestine(s), duplications.*

Defecation, infrequency, normal, in infants, *Feb.*, 127
Defecation reflex, *Feb.*, 128
Dehydration, *Feb.*, 57
Diagnosis and antimicrobial therapy in infections of respiratory tract, *May*, **353–67**
Diarrhea, *Feb.*, **137–52**; *May*, 408
as symptom of polyp, *Feb.*, 97
epidemic, of newborn, *Feb.*, 139
psychosomatic aspects, *Feb.*, 202
Diet in ulcerative colitis, *Feb.*, 157
Dihydrostreptomycin and streptomycin, applied pharmacology, *May*, **279–94**. See also under *Streptomycin.*
Dihydroxystilbamidine in histoplasmosis, *May*, 365
Diiodohydroxyquinoline in amebiasis, *Feb.*, 174; *May*, 415
Diodoquin. See *Diiodohydroxyquinoline.*
Diverticulum, Meckel's, rectal bleeding due to, *Feb.*, 211
Drug(s), reactions due to sulfonamide therapy, *May*, 243
relaxant, in proctologic anesthesia, *Feb.*, 62
Duapen. See *Benzathine penicillin G* under *Penicillin, preparations.*

Edema, cerebral. See *Cerebral edema.*
Emetine hydrochloride in amebiasis, *Feb.*, 174
Emotional disturbances, diarrhea due to, *Feb.*, 142
Emotional stress and physical symptoms, *Feb.*, 197
Encopresis, psychosomatic aspects, *Feb.*, 202
Endocarditis, bacterial, subacute, *May*, 403–5
bacteriology, *May*, 404
diagnosis, *May*, 404
frequency, *May*, 403
prevention, *May*, 405
treatment, *May*, 404

Endoscopy, *Feb.*, 18
anesthesia for, *Feb.*, 20
position for, *Feb.*, 21
preparation, *Feb.*, 19
technique, *Feb.*, 21
Endotrachea, intubation, in proctologic surgery, *Feb.*, 62
Enemas, administration, *Feb.*, **191–6**
contraindications, *Feb.*, 195
precautions, *Feb.*, 193
cleansing, *Feb.*, 192
diagnostic, *Feb.*, 192
effectiveness of, judging, *Feb.*, 195
preparation of child for, *Feb.*, 192
preparatory, for endoscopy, *Feb.*, 19
therapeutic, *Feb.*, 192
Enteric cyst. See *Intestine(s), duplications.*
Enteritis, regional, *May*, 419
Enterobiasis. See *Oxyuriasis.*
Enterocolitis, pseudomembranous, *May*, 418
Enterogenous cyst. See *Intestine(s), duplications.*
Eruption, creeping. See *Larva migrans, cutaneous.*
Erythrocin. See *Erythromycin.*
Erythromycin, absorption, *May*, 308
administration, routes of, *May*, 310, 453, 455
and related compounds, applied pharmacology, *May*, **305–15**
antimicrobial properties, *May*, 307
applied pharmacology, *May*, 306–13
bacterial resistance, *May*, 313
chemical properties, *May*, 306
dosage, *May*, 310, 453
in cellulitis, *May*, 272
in diphtheria contacts, prophylactic, *May*, 275
in furunculosis, *May*, 272
in gastrointestinal tract infections, *May*, 414
in pulmonary infections, *May*, 364
in rheumatic fever prophylaxis, *May*, 309
in soft tissue abscess, *May*, 272
in urogenital tract infections, *May*, 373
indications, *May*, 308
physical properties, *May*, 306
preparations, *May*, 310
for parenteral use, *May*, 311
for topical use, *May*, 312
side effects, *May*, 312
tissue distribution, *May*, 308
toxicity, *May*, 312
Escherichia coli infections, *May*, 409
Esophagus, varices, rectal bleeding due to, *Feb.*, 210
Ether in proctologic anesthesia, *Feb.*, 59, 60
Ethyl vanillate in histoplasmosis, *May*, 365
Examination, proctologic, *Feb.*, **15–26.** See also *Proctologic examination.*

FECES, appearance, *Feb.*, 15
culture studies, *Feb.*, 25
impaction, *Feb.*, 75
Feeding in diarrhea, *Feb.*, 149
Ferric and ammonium citrate in whipworm infection, *Feb.*, 180
Fissure, anal, *Feb.*, 119
Fissure quadrad, *Feb.*, 121
Fistula, anal, *Feb.*, 122–4
as indication for operation in ulcerative colitis, *Feb.*, 161
rectoperineal, diagnosis, *Feb.*, 69
treatment, surgical, *Feb.*, 72, 73
recto-urethral, vs. rectovesical fistula, *Feb.*, 70
rectovaginal, diagnosis, *Feb.*, 69
treatment, surgical, *Feb.*, 73
rectovesical, treatment, surgical, *Feb.*, 72
vs. recto-urethral fistula, *Feb.*, 70
Fluid(s), in renal complications of sulfonamide therapy, *May*, 242
intravenous, administration, preoperative, *Feb.*, 58
therapy, preoperative, *Feb.*, 56
Forceps, biopsy, *Feb.*, 23
Foreign body, inserted, rectal bleeding due to, *Feb.*, 213
rectal bleeding due to, *Feb.*, 210
Fossa, ileoappendicular, *Feb.*, 7
ileocecal, *Feb.*, 7
intersigmoid, *Feb.*, 7
retrocolic, *Feb.*, 6
Fuadin. See *Stibophen.*
Fumadil. See *Fumagillin.*
Fumagillin in amebic dysentery, *May*, 416
Furadantin. See *Nitrofurantoin.*

GANTRISIN. See *Sulfisoxazole* under *Sulfonamides.*
Gastroenteritis, salmonella types in, *Feb.*, 143
Gastrointestinal tract, infections, antimicrobial therapy, *May*, **407–26**
bacterial, *May*, 407
treatment, *May*, 412
reactions, to antibiotics, *May*, 440
to chloramphenicol, *May*, 323

Gelatin solution as cleansing agent for enemas, *Feb.*, 191
Genitourinary tract, infections, antimicrobial therapy, *May*, **369–76**
Gentian violet, in oxyuriasis, *Feb.*, 183
in strongyloidiasis, *Feb.*, 185, 186
Glucose, in dehydration, *Feb.*, 57
in ketosis, *Feb.*, 57
Gramicidin, administration, routes of, *May*, 455

HEART disease, rheumatic, *May*, 399
Hemophilus influenzae meningitis, *May*, 381
Hemorrhage, anorectal, *Feb.*, 16
as indication for operation in ulcerative colitis, *Feb.*, 160
rectal, *Feb.*, **207–14**. See also *Rectum, bleeding from.*
Hemorrhoidal veins, *Feb.*, 8
Hemorrhoidal venous plexus, *Feb.*, 8
Hemorrhoids, *Feb.*, 116–7
Hernia, retroperitoneal, *Feb.*, 6
relation to colon, *Feb.*, 5
Hexylresorcinol in whipworm infection, *Feb.*, 180
Hirschsprung's disease (megacolon), *Feb.*, 39, 40, 87–90, 134–6
Histoplasmosis, *May*, 417
diagnosis, *May*, 358
treatment, *May*, 365
Hormone therapy, in ulcerative colitis, *Feb.*, 158
relation to antibiotic therapy, *May*, 231
Hospitalization for ulcerative colitis, *Feb.*, 157
Host-drug-pathogen interactions, *May*, 230
Hydrochloric acid. See under *Acid.*
Hydrocortisone. See under *Adrenocortical preparations.*

ILEAL membrane, Lane's, *Feb.*, 4
Ileitis, backwash, *Feb.*, 154, 165
Ileoappendicular fossa, *Feb.*, 7
Ileocecal fossa, *Feb.*, 7
Ileum duplex. See *Intestine(s), duplications.*
Iliotycin. See *Erythromycin.*
Inclusion cyst. See *Intestine(s), duplications.*
Infection, intestinal, vs. intoxication, *Feb.*, 143
parenteral, diarrhea complicating, *Feb.*, 141
pinworm. See *Oxyuriasis.*
Infection, resistant to antibiotics, management, *May*, 348
size of, as prognostic factor in tuberculosis, *May*, 428
whipworm, *Feb.*, 178–80
Influenza, diagnosis, *May*, 354
INH. See *Isoniazid.*
Intercolic membranes, *Feb.*, 5
Intersigmoid fossa, *Feb.*, 7
Intestinal tract, parasitoses, protozoan and metazoan, *Feb.*, **169–90**
Intestine(s), diverticula, Meckel's, rectal bleeding due to, *Feb.*, 211
duplications, *Feb.*, 85–7
rectal bleeding due to, *Feb.*, 210
intoxication, treatment, *Feb.*, 146
vs. infection, *Feb.*, 143
large, malignancy, *Feb.*, 105–8
obstruction, as symptom of polyp, *Feb.*, 96
small, involvement in ulcerative colitis, effect on prognosis, *Feb.*, 165
volvulus, *Feb.*, 84
rectal bleeding due to, *Feb.*, 211
roentgen study, *Feb.*, 36
Intra-abdominal bands or membranes, *Feb.*, 4
Intoxication, intestinal. See under *Intestine(s).*
Intussusception, rectal bleeding due to, *Feb.*, 211
roentgen study, *Feb.*, 50
sigmoid, recurrent, chronic, rectal bleeding due to, *Feb.*, 212
vs. rectal procidentia, *Feb.*, 117, 118
Isoniazid, absorption, *May*, 250
administration, *May*, 251
chemistry, *May*, 250
distribution, *May*, 250
dosage, *May*, 251
excretion, *May*, 250
historical account, *May*, 249
in meningitis, *May*, 251
in tuberculosis, *May*, 251, 365, 429, 432, 434
in tuberculous meningitis, *May*, 251, 435
pharmacodynamic action, *May*, 250
toxicity, *May*, 251
Isonicotinic acid hydrazide. See *Isoniazid.*

JACKSON'S membrane, *Feb.*, 4
Jejunal membranes, mesocolic, *Feb.*, 4
Joints, tuberculosis of, *May*, 436

KETOSIS, *Feb.*, 57

Kidneys, complications of sulfonamide therapy, *May*, 241
causes, *May*, 241
diagnosis, *May*, 242
prevention, *May*, 243
signs, *May*, 241
treatment, *May*, 242
reactions to antibiotics, *May*, 441

LANE'S ileal membrane, *Feb.*, 4
Larva migrans, cutaneous, due to *Strongyloides*, *Feb.*, 185
Laryngitis, diagnosis, *May*, 360
Lavage, gastric, in tuberculosis, *May*, 431
Leche de higuerón in whipworm infection, *Feb.*, 180
Levophed in Waterhouse-Friderichsen syndrome, *May*, 392
Liver, involvement due to chloramphenicol, *May*, 324
reactions to antibiotics, *May*, 442
Lungs, infections, treatment, *May*, 363
roentgenogram in tuberculosis, *May*, 430
Lymph nodes, hilar, enlarged, and positive tuberculin test, *May*, 433
Lymphadenitis, cervical, *May*, 433
Lymphatic drainage of cecum and colon, *Feb.*, 7

MAGNAMYCIN. See *Carbomycin*.
Magnesia, milk of, in constipation, *Feb.*, 127
Mandelic acid. See under *Acid*.
Manson's schistosomiasis, *Feb.*, 186-8
Meckel's diverticulum. See under *Intestine(s), diverticula*.
Membranes, intra-abdominal, *Feb.*, 4
Meninges, subdural effusion, management, *May*, 390
Meningitis, bacterial, clinical syndrome, *May*, 378
complications, recognition and treatment, *May*, 390
diagnosis, early, relation to treatment, *May*, 383
differential diagnosis, *May*, 379
management, *May*, **377-98**
treatment, *May*, 383
antibiotic, specific, *May*, 384
general supportive measures, *May*, 383
Hemophilus influenzae, *May*, 381
meningococcal, *May*, 381
pneumococcal, *May*, 382
purulent, acute, incidence, *May*, 378
tuberculous, *May*, 435
Meningococcal meningitis, *May*, 381
Meningococcemia, fulminating, *May*, 382
recognition and treatment, *May*, 392
Mesentery, cysts, relation to colon, *Feb.*, 5
thrombosis, rectal bleeding due to, *Feb.*, 211
Mesocolic cyst, *Feb.*, 5
Mesocolic jejunal membranes, *Feb.*, 4
Metabolism, alterations in, due to diarrhea, *Feb.*, 143
Metazoan and protozoan parasitoses of intestinal tract, *Feb.*, **169-90**
Milibis. See *Bismuth glycolylarsenilate*.
Milk of magnesia in constipation, *Feb.*, 127
Moniliasis. See *Candidiasis*.
Mononucleosis, infectious, diagnosis, *May*, 357
Morphine, preanesthetic use, *Feb.*, 59
Muscles, relaxants in proctologic anesthesia, *Feb.*, 62
Mycifradin. See *Neomycin*.
Mycostatin. See *Nystatin*.
Mycotic infections, *May*, 416

NEOMYCIN, *May*, 336
absorption, *May*, 338
administration, *May*, 338
intramuscular, *May*, 338
oral, *May*, 338
routes of, *May*, 454, 455
topical, *May*, 339
antimicrobial activity, *May*, 337
bacitracin and polymyxin, applied pharmacology, *May*, **329-44**
clinical use, *May*, 339
dosage, *May*, 338, 454
excretion, *May*, 338
in bacillary infections, *May*, 339
in conjunctivitis, *May*, 339, 340
in eczema, *May*, 339, 340
in gastrointestinal tract infections, *May*, 413
in intestinal infections, *May*, 339
in pyogenic dermatoses, *May*, 339
in shigellosis, *May*, 336
in urinary tract infections, *May*, 339
in urogenital tract infections, *May*, 373
preoperative use, *May*, 339
toxicity, *May*, 337
Neoplasms, of colon and rectum, *Feb.*, **93-111**
rectal bleeding due to, *Feb.*, 213
Nervous system, autonomic, of colon and rectum, *Feb.*, 9
central, disease, cerebrospinal fluid changes in, *May*, 380

Neurologic reactions to chloramphenicol, *May*, 323
Newborn, epidemic diarrhea, *Feb.*, 139
Nitrofurantoin, absorption, *May*, 253
  administration, routes of, *May*, 454, 455
  chemistry, *May*, 252
  dosage, *May*, 454
  excretion, *May*, 253
  historical account, *May*, 252
  in urogenital tract infections, *May*, 372
  pharmacodynamic action, *May*, 252
  toxicity, *May*, 254
Nitrous oxide in proctologic anesthesia, *Feb.*, 59, 61
Nutrition in ulcerative colitis, *Feb.*, 157
Nystatin, administration, routes of, *May*, 454, 455
  dosage, *May*, 454
  in candidiasis, *May*, 418
  in coccidioidomycosis, *May*, 365

Obstipatio paradoxica, *Feb.*, 131
Omphalocele, *Feb.*, 83
Ornithosis. See *Psittacosis*.
Oxygen, postoperative, in proctology, *Feb.*, 64
Oxygenation in proctologic anesthesia, *Feb.*, 55
Oxytetracycline, absorption, *May*, 297, 298, 299
  administration, *May*, 298, 299
    routes of, *May*, 452, 455
  chemical differentiation, *May*, 297
  dosage, *May*, 298, 299, 452
  in cystic fibrosis of pancreas, *May*, 302
  in meningitis, *May*, 386, 387, 388
  in urogenital tract infections, *May*, 373
  mechanism of action, *May*, 228
  stability, *May*, 296
  toxicity, *May*, 301
Oxyuriasis, *Feb.*, 180–4

PA 105, *May*, 314
Pain, anorectal, *Feb.*, 16
Pancydine. See *Tetracycline(s)*.
Panmycin. See *Tetracycline(s)*.
PAP. See *Pneumonia, atypical, primary*.
Papanicolaou smear technique in proctologic examination, *Feb.*, 24
Papillitis, *Feb.*, 119
Para-aminosalicylic acid. See under *Acid*.
Paracolon infections, *May*, 411
Parasitoses, protozoan and metazoan, of intestinal tract, *Feb.*, **169–90**
Parenteral infections, diarrhea complicating, *Feb.*, 141

PAS. See *Acid, para-aminosalicylic*.
Pelvirectal sphincter, *Feb.*, 12
Penicillin, absorption, *May*, 261
  administration, intramuscular, effect on absorption, *May*, 262
  oral, *May*, 266
    effect on absorption, *May*, 261
  parenteral, *May*, 267
  routes of, *May*, 265, 452, 455
  antagonism to broad-spectrum antibiotics, *May*, 269
  applied pharmacology, *May*, **259–77**
  bacterial resistance, *May*, 269
  chemistry, *May*, 260
  dosage, *May*, 265, 452
  forms, *May*, 266
  massive, effect of, *May*, 270
  weight vs. unitage, *May*, 270
  effect of tissue constituents on, *May*, 261
  efficiency, enhancement by cobalt, *May*, 226
  in cellulitis, *May*, 272
  in congenital syphilis, *May*, 275
  in diphtheria contacts, prophylactic, *May*, 275
  in fulminating meningococcemia, *May*, 275, 393
  in furunculosis, *May*, 272
  in gonococcal infections, *May*, 274
  in mastoiditis, *May*, 273
  in meningitis, *May*, 272, 274, 386, 387, 388, 389, 390
  in meningococcal infections, *May*, 274
  in meningococcus contacts, prophylactic, *May*, 275
  in ophthalmia of newborn, *May*, 274
  in oral surgery, prophylactic, *May*, 275
  in ornithosis, *May*, 361, 362
  in osteomyelitis, *May*, 272
  in otitis media, *May*, 273
  in pneumococcal infections, *May*, 274
  in pneumonia, *May*, 272, 274, 363
  in pulmonary infections, *May*, 364
  in respiratory infections, *May*, 273
  in rheumatic fever prophylaxis, *May*, 275, 402, 452
  in scarlet fever, *May*, 273
    contacts, prophylactic, *May*, 275
  in soft tissue abscess, *May*, 272
  in staphylococcal infections, *May*, 272
  in streptococcal infections, *May*, 273, 401
  in subacute bacterial endocarditis, *May*, 273, 405

Penicillin, in urethritis, *May*, 274
in urogenital tract infections, *May*, 372
in vulvovaginitis, *May*, 274
indications, *May*, 271
mechanism of action, *May*, 224
physical properties, *May*, 260
preparations, aqueous crystalline penicillin, absorption, *May*, 262
benzathine penicillin G, absorption, *May*, 262
chemistry, *May*, 260
parenteral administration, *May*, 268
crystalline aqueous penicillin G, parenteral administration, *May*, 267
penicillin G, absorption, *May*, 261
procaine penicillin G, absorption, *May*, 262
chemistry, *May*, 260
parenteral administration, *May*, 267
penicillin O, chemistry, *May*, 260
penicillin V, absorption, *May*, 262
chemistry, *May*, 260
prophylactic indications, *May*, 276
reactions, accidental, *May*, 442
anaphylactic, *May*, 440
side effects, *May*, 264
solubility, *May*, 261
source, *May*, 260
staphylococcal resistance to, *May*, 268
therapy, current, general comments on, *May*, 268
tissue distribution, *May*, 263
toxicity, *May*, 264
unitage, *May*, 261
use, indiscriminate, in pediatrics, *May*, 270
Peptic ulcer, rectal bleeding due to, *Feb.*, 211
Perforation as indication for operation in ulcerative colitis, *Feb.*, 160
Periappendicular membranes, *Feb.*, 4
Permapen. See *Benzathine penicillin G* under *Penicillin, preparations*.
Peutz-Jegher syndrome, *Feb.*, 102
Phenol, in rectal procidentia, *Feb.*, 119
in rectal prolapse, *Feb.*, 118
Phthalylsulfathiazole, dosage, *May*, 245
Pinworm infection. See *Oxyuriasis*.
Piperazine hexahydrate in oxyuriasis, *Feb.*, 183
Pneumococcal meningitis, *May*, 382
Pneumonia, atypical, primary, treatment, *May*, 362
treatment, *May*, 363
Pneumoperitoneum, roentgen examination, *Feb.*, 29
Poliomyelitis, 1956, *May*, **457–81**
Polycycline. See *Tetracycline(s)*.
Polymyxin, *May*, 329
absorption, *May*, 332
administration, *May*, 333
intramuscular, *May*, 333
intrathecal, *May*, 334
oral, *May*, 334
routes of, *May*, 453, 455
topical, *May*, 334
antimicrobial activity, *May*, 330
clinical use, *May*, 334
distribution, *May*, 332
dosage, *May*, 333, 453
excretion, *May*, 332
in meningitis, *May*, 334, 335
in pyelonephritis, *May*, 335
in Shigella infections, *May*, 413
in shigellosis, *May*, 335
in superficial infections, *May*, 336
in systemic infections, *May*, 336
in urogenital tract infections, *May*, 373
local pain at site of injection, *May*, 331
mechanism of action, *May*, 229
neomycin and bacitracin, applied pharmacology, *May*, **329–44**
nephrotoxicity, *May*, 332
neurotoxicity, *May*, 331
preoperative use, *May*, 339
toxicity, *May*, 331
Polyposis, of colon, *Feb.*, 101. See also *Colon, polyposis*.
rectal bleeding due to, *Feb.*, 212
Polyps, of colon and rectum, *Feb.*, 94–101
rectal bleeding due to, *Feb.*, 212
Pontocaine. See *Tetracaine*.
Potassium and antimony tartrate. See *Tartar emetic*.
Potassium chloride solution. See under *Solution*.
Potassium depletion, *Feb.*, 58
Potassium lactate in Waterhouse-Friderichsen syndrome, *May*, 393
Procaine in proctologic anesthesia, *Feb.*, 63, 64
Procaine hydrochloride in anal fissure, *Feb.*, 121
Procaine penicillin G. See under *Penicillin, preparations*.
Proctologic examination, *Feb.*, **15–26**
diagnostic procedures, *Feb.*, 25
proctoscopic, *Feb.*, 17
recto-abdominal, *Feb.*, 17

Proctologic lesions, psychosomatic aspects, *Feb.*, **197–206**
Proctology, anesthesia for, *Feb.*, **53–66**. See also *Anesthesia for proctology*.
symposium on, *Feb.*, **1–214**
Proctoscope, *Feb.*, 19
in diagnosis of polyps of colon and rectum, *Feb.*, 97, 98
Proteus infections, *May*, 411
Protozoan and metazoan parasitoses of intestinal tract, *Feb.*, **169–90**
Protozoan infection, *May*, 414
Pseudomonas infections, *May*, 411
Psittacosis, diagnosis, *May*, 358
treatment, *May*, 361
Psychosomatic aspects of proctologic lesions, *Feb.*, **197–206**
Psychotherapy in ulcerative colitis, *Feb.*, 159

Q FEVER, diagnosis, *May*, 358
Quinine urea hydrochloride, in rectal procidentia, *Feb.*, 119
in rectal prolapse, *Feb.*, 118

RECTOPERINEAL fistula. See under *Fistula*.
Recto-urethral fistula vs. rectovesical fistula, *Feb.*, 70
Rectovaginal fistula. See under *Fistula*.
Rectovesical fistula. See under *Fistula*.
Rectum. See also *Anorectum* and *Anus*.
abnormalities, congenital, *Feb.*, 13
anatomy, *Feb.*, 94
and colon, anatomy, applied, *Feb.*, **3–13**
neoplasms, *Feb.*, **93–111**
bleeding from, *Feb.*, **207–14**
as symptom of polyp, *Feb.*, 96
dilatations, *Feb.*, 74
instillations, in ulcerative colitis, *Feb.*, 159
nervous system, autonomic, *Feb.*, 9
perforation, roentgen examination, *Feb.*, 29
polyps, *Feb.*, 94–101
procidentia, *Feb.*, 117–9
prolapse, *Feb.*, 117–9
sphincters, *Feb.*, 12
venous return of blood from, *Feb.*, 8
Reflex, defecation, *Feb.*, 128
Relaxants. See under *Muscles*.
Respiratory tract, disease, acute, undifferentiated, diagnosis, *May*, 355, 356
age factors, *May*, 359
clinical spectrum, *May*, 359
Respiratory tract, disease, diagnosis, *May*, 358
primary, *May*, 359
secondary, *May*, 359
viral, treatment, *May*, 362
infections, acute, types and etiology, *May*, 354
bacterial, treatment, *May*, 363
diagnosis, *May*, 353
and antimicrobial therapy, *May*, **353–67**
treatment, *May*, 361
Retrocolic fossa, *Feb.*, 6
Retroperitoneal cyst, *Feb.*, 5
Retroperitoneal hernia. See under *Hernia*.
Rheumatic fever, *May*, 399
prevention in patients with previous rheumatic fever, *May*, 402
preventive measures, *May*, 402
streptococcal infection in, importance, *May*, 399
RI 67 virus infections, diagnosis, *May*, 355, 356
Rickettsial diseases, diagnosis, *May*, 357
treatment, *May*, 361
Ringer's solution. See under *Solution*.
Roentgenology of colon, *Feb.*, **27–52**

SACRAL vein, *Feb.*, 9
Salmonella, infections, *May*, 409
types in gastroenteritis, *Feb.*, 143
Schistosomiasis, Manson's, *Feb.*, 186–8
other forms, *Feb.*, 188
Scopolamine, preanesthetic use, *Feb.*, 59
Secobarbital, preanesthetic use, *Feb.*, 59
Sedation in ulcerative colitis, *Feb.*, 157
Shigella infections, *May*, 409
Sigmoidoscope, *Feb.*, 18
Skin reactions to chloramphenicol, *May*, 322
Skin test, tuberculin, *May*, 430
Sodium bicarbonate in renal complications of sulfonamide therapy, *May*, 242
Sodium biphosphate for colon catharsis, *Feb.*, 20
Sodium lactate in acidosis, *Feb.*, 57
Sodium phosphate for colon catharsis, *Feb.*, 20
Solution, gelatin, as cleansing agent for enemas, *Feb.*, 191
potassium chloride, in diarrhea, *Feb.*, 147
potassium chloride-Ringer's, in potassium depletion, *Feb.*, 58
Ringer's, in alkalosis, *Feb.*, 57
in dehydration, *Feb.*, 57
in Waterhouse-Friderichsen syndrome, *May*, 392

Solution, Ringer's lactate, in diarrhea, *Feb.*, 146, 147
in meningitis, *May*, 385
saline, for endoscopy, *Feb.*, 19
in dehydration, *Feb.*, 57
Sphincters of rectum, *Feb.*, 12
Spiramycin, *May*, 314
Staphylococci, penicillin-resistant, *May*, 268
resistance to antibiotics, *May*, 346
infections due to, gastrointestinal, *May*, 412
Steclin. See *Tetracycline(s)*.
Stibophen in Manson's schistosomiasis, *Feb.*, 188
Stool. See *Feces*.
Streptococcal infections, danger of, *May*, 402
diagnosis, *May*, 400
frequency, *May*, 400
importance in rheumatic fever, *May*, 399
treatment, *May*, 401
Streptomycin, absorption, *May*, 281
action, mode of, *May*, 281
activity in vitro, *May*, 287
administration, *May*, 283
routes of, *May*, 452, 455
and dihydrostreptomycin, applied pharmacology, *May*, **279–94**
bacterial dependence on, *May*, 289
bacterial resistance to, *May*, 288
blood levels, *May*, 284
chemistry, *May*, 280
complications of therapy, *May*, 285
dihydrostreptomycin, absorption, *May*, 283
administration, routes of, *May*, 452, 455
chemistry, *May*, 281
distribution, *May*, 283
dosage, *May*, 452
excretion, *May*, 283
in subacute bacterial endocarditis, *May*, 405
in tuberculous meningitis, *May*, 435
in urogenital tract infections, *May*, 373
source, *May*, 279
vestibular-auditory disturbances due to, *May*, 286
distribution, *May*, 282
dosage, *May*, 283, 452
excretion, *May*, 282
hypersensitivity reactions, *May*, 285
in meningitis, *May*, 386, 387, 388
in pneumonia, *May*, 363
Streptomycin, in pulmonary infections, *May*, 364, 365
in subacute bacterial endocarditis, *May*, 405
in tuberculosis, *May*, 290, 365, 428, 429, 434
in tuberculous meningitis, *May*, 435
in urogenital tract infections, *May*, 373
indications, *May*, 289
intrathecal irritation, *May*, 286
mechanism of action, *May*, 224
potentiation by combination, *May*, 291
source, *May*, 279
urinary levels, *May*, 284
vestibular-auditory disturbances due to, *May*, 286
Streptonivicin, *May*, 313
in pulmonary infections, *May*, 364
Stress, emotional, and physical symptoms, *Feb.*, 197
Strongyloidiasis, *Feb.*, 184–6
Subdural. See under *Meninges*.
Succinylcholine in proctologic anesthesia, *Feb.*, 62
Succinylsulfathiazole. See under *Sulfonamides*.
Sulfadiazine. See under *Sulfonamides*.
Sulfamerazine. See under *Sulfonamides*.
Sulfamethazine. See under *Sulfonamides*.
Sulfanilamide. See under *Sulfonamides*.
Sulfapyrimidines. See *Sulfadiazine*, *Sulfamerazine*, *Sulfamethazine*, under *Sulfonamides*.
Sulfasuxidine. See *Succinylsulfathiazole* under *Sulfonamides*.
Sulfathalidine. See *Phthalylsulfathiazole*.
Sulfisoxazole. See under *Sulfonamides*.
Sulfonamides, absorption, *May*, 238
administration, *May*, 244
routes of, *May*, 454, 455
chemistry, *May*, 237
contraindications, *May*, 246
distribution, *May*, 238
dosage, *May*, 244, 454
excretion, *May*, 238
historical account, *May*, 235
in mastoiditis, *May*, 273
in meningitis, *May*, 388
in otitis media, *May*, 273
in rheumatic fever prophylaxis, *May*, 402
in urogenital tract infections, *May*, 372
indications, *May*, 245
mixtures, *May*, 240
dosage, *May*, 245
pharmacodynamic action, *May*, 237
reactions, toxic, mild, *May*, 240

Sulfonamides, reactions, toxic, severe, *May*, 241
succinylsulfathiazole, dosage, *May*, 245
sulfadiazine, administration, *May*, 244
routes of, *May*, 454
dosage, *May*, 245, 454
in fulminating meningococcemia, *May*, 275, 393
in meningitis, *May*, 245, 274, 385, 387, 389
in meningococcemia, *May*, 274
in pulmonary infections, *May*, 364
in rheumatic fever prophylaxis, *May*, 402
sulfamerazine, administration, *May*, 244
routes of, *May*, 454
dosage, *May*, 245, 454
sulfamethazine, administration, *May*, 244
dosage, *May*, 245
sulfanilamide, administration, *May*, 244
dosage, *May*, 245
sulfisoxazole, administration, routes of, *May*, 454
dosage, *May*, 454
in urogenital tract infections, *May*, 372
toxicology, *May*, 240
use, *May*, 451
Symptoms, physical, and emotional stress, *Feb.*, 197
Systemic disease, rectal bleeding due to, *Feb.*, 212

TANNIC acid. See under *Acid*.
Tartar emetic in Manson's schistosomiasis, *Feb.*, 188
Terramycin. See *Oxytetracycline*.
Tetracaine in proctologic anesthesia, *Feb.*, 63
Tetracycline(s). See also *Chlortetracycline*; *Oxytetracycline*.
absorption, *May*, 297
administration, *May*, 297
routes of, *May*, 452, 453, 454
applied pharmacology, *May*, **295–303**
chemical differentiation, *May*, 297
dosage, *May*, 297, 452, 453
excretion, *May*, 297
in cystic fibrosis of pancreas, *May*, 302
in fulminating meningococcemia, *May*, 275
in meningeal infections, *May*, 299
in meningitis, *May*, 386, 387, 388, 389
in ornithosis, *May*, 361, 362
in pneumonia, *May*, 363
Tetracycline(s), in pneumonia, primary atypical, *May*, 362
in pulmonary infections, *May*, 364, 365
in rickettsial diseases, *May*, 361
in urogenital tract infections, *May*, 373
mechanism of action, *May*, 228
preoperative use, *May*, 339
solubility, *May*, 296
source, *May*, 295
stability, *May*, 296
toxicity, *May*, 300
Tetracyn. See *Tetracycline(s)*.
Thorax, cysts. See *Intestine(s), duplications*.
Thrombosis, mesenteric, rectal bleeding due to, *Feb.*, 211
Tissue constituents, effect on penicillin, *May*, 261
Toxemia, fulminating, acute, as indication for operation in ulcerative colitis, *Feb.*, 160
Toxicology of antibiotics, *May*, **439–45**
Trichlorethylene in proctologic anesthesia, *Feb.*, 61
Tuberculin test, *May*, 430
evaluation, *May*, 430
positive, and enlarged hilar lymph nodes, *May*, 433
without radiologic evidence of disease, *May*, 431
Tuberculosis, chemotherapy, general considerations, *May*, 428
contact, history of, *May*, 431
diagnosis, *May*, 358
hematogenous, protracted, *May*, 434
in children, at puberty, *May*, 432
up to puberty, *May*, 432
in infants, *May*, 431
infectiousness, *May*, 437
miliary, *May*, 434
of bones and joints, *May*, 436
patient with, removal from infectious contacts, *May*, 436
physical examination, *May*, 431
practical management, *May*, **427–38**
problems, special, *May*, 436
prognostic factors, important, *May*, 427
pulmonary, primary, progressive, *May*, 434
source, *May*, 436
symptoms, *May*, 431
treatment, *May*, 365
vaccine, BCG, for tuberculosis contacts, *May*, 437
Tubocurarine hydrochloride in proctologic anesthesia, *Feb.*, 62

Tumors of colon, roentgen study, *Feb.*, 46
polypoid, roentgen study, *Feb.*, 43
Tyrothricin, administration, routes of, *May*, 454, 455
dosage, *May*, 454
mechanism of action, *May*, 229

Ulcer, peptic. See *Peptic ulcer.*
Urinary tract, infections, diagnosis, *May*, 371
etiologic considerations, *May*, 369
symptoms, *May*, 371
treatment, *May*, 374
Urine, examination, *May*, 371

Varices, esophageal, rectal bleeding due to, *Feb.*, 210
Viocin. See *Viomycin.*
Viomycin, administration, routes of, *May*, 454, 455
dosage, *May*, 454
in tuberculosis, *May*, 429
Vitamin(s), deficiency, due to antibiotics, *May*, 443
Volvulus. See under *Intestine(s).*

Waterhouse-Friderichsen syndrome. See *Meningococcemia, fulminating.*
Whipworm infection, *Feb.*, 178-80